THE CONTROL OF SPATIALLY CONSTRAINED UNILATERAL AND BILATERAL MOVEMENTS: HEMISPHERIC AND CALLOSAL CONTRIBUTIONS

By

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ABSTRACT

When a person performs an arm movement that requires concurrent activity of the contralateral arm, it is common to observe a decrement in performance relative to when the same task is performed in isolation (Ohtsuki, 1994). Thus, if a task requires a rapid movement of one arm, that movement will, in general, be executed more quickly compared with a condition where the opposite arm is moved simultaneously (Fowler et al., 1991; Marteniuk & MacKenzie, 1980). Reaction time is similarly affected when simultaneous bilateral actions are performed, with bilateral movements requiring more time for movement initiation (Anson & Bird, 1993; Ohtsuki, 1994). Recently it has been suggested that the increase in reaction time accompanying bilateral movements might reflect an inhibitory interaction between the motor cortexes of the left and right hemispheres through the corpus callosum, resulting in an increase in the time required for muscle activation (Ohtsuki, 1994). Recent studies have provided support for this interpretation (Meyer & Voss, 2000; Taniguchi et al., 2001).

Despite empirical support, however, a number of studies have yielded results inconsistent with this proposal in that bilateral movements did not lead to increases in reaction time (Anson & Bird, 1993; Swinnen et al., 1995). We (Garry & Franks, 2000) also reported a failure for reaction time to increase with bilateral movements, but only when the task demanded spatial precision of the right arm. When left arm precision was required, reaction time increases were observed. Because our task involved proximal muscles, which can be controlled through ipsilateral pathways (Berlucchi et al., 1994; Brinkman & Kuypers, 1973), we interpreted this result as evidence that under certain conditions (right arm precision), bilateral movements can be initiated via a single hemisphere eliminating the
inhibitory interhemispheric interactions that accompany bilateral movements. Although experiments 1 and 2 were consistent with the predictions of this model, experiment 3 failed to provide support. An alternative model involving premotor cortex mechanisms was proposed.
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CONTRIBUTIONS OF THE AUTHORS

This thesis contains three separate studies that have been undertaken by the candidate, Michael Garry, under the supervision of Ian M. Franks (Professor, Human Kinetics). Each study is the primary ownership of the candidate.

The above statement was written by Michael Garry and agreed upon by the undersigned.

Ian M. Franks

References


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1. Introduction

Numerous studies have been conducted comparing motor performance during unilateral tasks with bilateral task performance. Performance measures investigated have included strength (Howard & Enoka, 1991; Li et al., 2000; Oda & Moritani, 1996; Schantz et al., 1989; Seki & Ohtsuki, 1990), movement kinematics, such as movement speed and movement time (Corcos, 1984; Kelso, Southard & Goodman, 1979; 1983; Marteniuk & MacKenzie, 1980; Marteniuk, MacKenzie & Baba, 1984), and reaction time (Aglioti et al., 1993; Anson & Bird, 1993; Di Stefano et al., 1980; Garry & Franks, 2000; Ohtsuki, 1981b; Taniguchi et al., 2001). Considered as a whole, these studies suggest that bilateral movements are associated with a decrement in performance relative to unilateral movements (see Ohtsuki, 1994).

Of particular interest to this thesis is the influence of bilateral performance on reaction time. As with other performance measures, reaction time often suffers when bilateral movements are executed. This is reflected by an increase in reaction time relative to unilateral movements. Recently, it has been suggested that a neural mechanism, transcallosal inhibition, might mediate this increase (Ohtsuki, 1994)—a proposal supported by several lines of research (Gazzaniga & Sperry, 1966; Meyer & Voss, 2000; Taniguchi et al., 2001). Despite empirical support there have been a number of studies whose results appear inconsistent with this mechanism (e.g., Anson & Bird, 1993; Swinnen et al., 1995). However, we (Garry & Franks, 2000) have recently proposed a model integrating transcallosal inhibition and ipsilateral motor control that might account for these discrepant observations. The experiments conducted in this thesis were designed to pursue this model in greater detail. Assumptions of the model were assessed, using both behavioural and
electrophysiological techniques, to determine if it can provide a sufficient account for the
influence of bilateral task performance on reaction time.

1.1. The bilateral deficit

An area of research that has garnered a great deal of interest with respect to bilateral
performance decrements is the bilateral deficit. The bilateral deficit describes, commonly, a
decrement in strength observed when simultaneous bilateral muscle contractions are
performed (Ohtsuki, 1994). A typical experiment involves an individual exerting a maximal
effort with each limb in isolation, and then repeating the effort with both limbs
simultaneously. The measure of interest is the ratio of the total force exerted by the bilateral
effort and the sum of the forces exerted by both limbs alone. In one study, Schantz et al.
(1989) had subjects perform a leg extension task. Subjects were seated in a chair and pressed
their feet against a foot-plate positioned directly in front of them. The position of the plate
was adjusted such that the knee was maintained at an angle of 90°. The total force exerted
during bilateral leg extensions was only 90% of that achieved during unilateral efforts. In
order to test whether the deficit in force was the result of an inability of the central nervous
system to activate a large number of muscles simultaneously, they had the subjects repeat the
experiment while holding a 125 N dumb-bell in each arm. Presumably, if the deficit were a
general effect of having to contract multiple muscles simultaneously then supporting weights
with the arms should increase the observed deficit. Contrary to this expectation, however,
the bilateral deficit remained unchanged. Thus, it was concluded that the force deficit was
not due to a general deficiency of the CNS to simultaneously activate multiple muscle
groups.
Another study by Howard and Enoka (1991) also demonstrated a bilateral deficit using a knee extension task. Subjects were seated on a bench with their legs extending beyond the end allowing flexion of the knees. Load cells were attached to the ankle to measure the force exerted during attempted knee extension. For untrained subjects, bilateral knee extensions yielded a deficit of approximately 10% relative to unilateral knee extension. In order to test whether the deficit was restricted to contraction of homologous muscle groups, a second task was performed which required simultaneous extension of the right knee and flexion of the left arm. No evidence of a force deficit was obtained for either muscle group. Consistent with the conclusion of Schantz et al. (1989), this finding appears to rule out the possibility that the bilateral deficit is the result of the CNS’s inability to maximally activate multiple groups of muscles. Rather, the results suggest that the deficit is due to intrinsic mechanisms associated with bilateral contraction of homologous muscle groups.

The bilateral deficit is not restricted to the muscles of the lower body. Several studies have reported similar deficits accompanying contractions of arm and hand muscles. Ohtsuki (1983) required subjects to perform unilateral and bilateral isometric elbow flexions by pulling against a chain attached to a force transducer. In a second condition elbow extension movements were performed while in a third condition an extension was performed with one arm while a flexion was performed with the other. For both symmetric contraction conditions (flexion-flexion and extension-extension) a bilateral deficit was observed. Bilateral flexion had a deficit of approximately 7% while for extension it was approximately 22%. However, no deficit was observed when the asymmetrical (flexion-extension) movement was performed supporting the conclusion of Howard and Enoka (1991) that the force deficit occurs when homologous muscle groups are contracted. In addition to force,
muscle activity levels were also measured. During bilateral performance, integrated EMG was significantly lower than for unilateral contractions suggesting that the deficit in force was not the result of biomechanical factors, but was due to an inability to maximally activate the muscle. Grip strength has also been found to suffer when bilateral contractions are performed (Ohtsuki, 1981a). During bilateral isometric hand-grip, maximal force was reduced by approximately 9%. Again, integrated EMG was measured and found to decrease in similar manner.

An analogue to the bilateral deficit has also been observed when submaximal contractions are performed. Seki and Ohtsuki (1990) had subjects perform unilateral and bilateral contractions to maintain a pre-determined percentage of their maximal unilateral force. The target forces were 25%, 50%, 75% and 100%. Because no feedback regarding the actual force produced was provided during the contraction, it was necessary to subjectively estimate the force exerted. At all levels of target force, the magnitude of force exerted during bilateral contractions was lower than that produced during unilateral contractions. A similar result was obtained in a more recent study by Oda and Moritani (1996). In this study, subjects performed both a unilateral and bilateral isometric hand-grip task to maintain a target level of force (20% MVC). When bilateral contractions were performed, forces were reduced relative to unilateral movements. Thus, even when the required magnitude of force is well below maximal, bilateral contractions are executed with a lower level of total force than are unilateral contractions.

1.2. Dynamic bilateral movements

A number of investigations have been conducted comparing performance between bilateral and unilateral movements. It is a common observation from these studies that
bilateral performance is reduced relative to unilateral performance. One variable that is consistently found to suffer when bilateral movements are performed is movement speed. Wyke (1969, 1971) tested subjects on their ability to perform a unilateral and bilateral tapping task involving the arms. In both studies, the number of taps performed was lower during bilateral movements than it was for unilateral movements. Wyke (1971) additionally compared unilateral and bilateral performance on a peg placement task and observed similar decrements.

A number of studies have also reported deficits in movement speed when rapid, bilateral aiming movements are performed. In their seminal paper, Kelso, Southard and Goodman (1979) investigated the differences between unilateral and bilateral aiming movements involving the arms that involved movements over different distances, and with different accuracy requirements. In one experiment, subjects were required to move their hands laterally away from the midline of the body to targets of various sizes positioned at different distances from the start position. In a second experiment, the targets remained at a fixed position near the body midline and the hands moved medially toward the targets from different starting positions. Finally, in a third experiment, the hands moved forwards away from the body to targets positioned at different distances from the start position. The major finding from these experiments was that when the two hands moved simultaneously, there was an overall tendency toward increased movement times relative to that of each hand performing alone. This was most apparent when the two hands traversed different distances. The hand traveling the shorter distance yielded increases in movement time relative to its performance over the same distance when moving alone. The result was a tight temporal coupling between the hands in the bilateral movement conditions, even when the tasks were
associated with large hand differences when performed alone. The authors suggested that the movements of both limbs were organized as a single unit, rather than as two separate units, with the performance of each arm being constrained primarily by the arm performing the more difficult (longer distance) movement. The author's conclusion was further supported by a second study (Kelso et al., 1983) in which the task required one hand to 'hurdle' a barrier positioned between the start position and the target region. Even though only one hand had to traverse the hurdle, the trajectories of both limbs were modified in this task.

Marteniuk and MacKenzie (1980) and Marteniuk et al. (1984) carried out a set of experiments similar to those conducted by Kelso et al. (1979), but with some notable differences in the movement tasks. In these studies, subjects were required to perform unilateral and bilateral movements over different distances to a point target 1 mm in diameter, rather than to targets of different sizes such as used by Kelso et al. (1979; 1983). In addition, subjects performed the movements using hand-held styli that were either light (50 grams) or heavy (350 grams). The results were similar to those of Kelso et al. (1979); when bilateral movements were performed movement time was increased relative to unilateral conditions. In addition, there was a noticeable effect on performance when the arms were executing different tasks. For example, when a short movement performed by one arm was paired simultaneously with a long movement of the other, the short movement slowed substantially. The end result was such that the movement times of the two arms during bilateral movements became quite similar compared with their respective unilateral performances. This effect was also observed when the arms executed the movements with different inertial loads; the lighter arm slowed down to more closely match the movement time of the heavier arm. While these results appear comparable to those of Kelso et al. (1979, 1983) it must be
pointed out that the two arms were never completely synchronous in their performance. This was a point of considerable theoretical importance to the authors and was used to differentiate their findings from those reported by Kelso et al. (1979, 1980). Differences in theoretical viewpoint notwithstanding, the series of experiments conducted by these two groups are consistent with performance deficits when bilateral movements are required. Similar observations have been made by several other groups (Corcos, 1984; Fowler et al., 1991; Honda, 1982; Stelmach & Worringham 1988).

1.3. Bilateral reaction time

Of interest to the present thesis is the influence of simultaneous bilateral performance on reaction time. As with strength and movement speed, reaction time is a performance variable that appears to suffer when bilateral movements are performed. Both the studies of Kelso et al. (1979, 1983) and Marteniuk and colleagues (1980, 1984) reported increased reaction time when bilateral movements were performed. Using a similar bilateral aiming task, Stelmach and Worringham (1988) observed that bilaterally symmetric arm movements took, on average, 37 ms longer to initiate than unilateral movements. This was the case both for healthy control subjects and for subjects with Parkinson’s disease. Fowler et al. (1991) had subjects perform unilateral and bilateral aiming movements over three different distances. The bilateral movements were performed either with the arms moving the same distance, or with the arms moving different distances. Again, when bilateral, symmetrical movements were performed (both arms travelling the same distance) reaction times were increased relative to unilateral movements, with the overall difference being approximately 15 ms.

The studies reported above have measured reaction time during tasks that require spatially precise movements, and as such, this has been a measure of secondary importance.
It is worthwhile asking whether similar results occur when reaction time is the primary variable of interest. Jeeves and Dixon (1970) had subjects perform a key press task in response to a visual stimulus. Responses were made unilaterally and bilaterally. It was observed that bilateral responses took, on average, 35 ms longer than unilateral responses. Greater bilateral reaction times were also observed by Ohtsuki (1981b) for a knee extension task. The increase was apparent for reaction time measured both by limb displacement and electromyographic muscle activity (EMG), which indicates when muscle activation first occurred. This latter measure is termed premotor time and is an indicator of central processing. The observation that premotor time increased suggests the effect is due to a central delay. In a more recent study, Anson and Bird (1993) reported longer bilateral reaction times for a finger extension task compared with unilateral movements. As with the study by Ohtsuki (1981b), this increase was observed for both premotor time and displacement reaction time. Considered together, it appears, that executing bilateral movements leads to deficits not only in measures of movement execution, but also movement initiation. With respect to reaction time, what processes might be responsible for this increase when bilateral movements are performed?

One possibility is that the mechanical differences between bilateral and unilateral movements might require different postural adjustments prior to movement initiation. This could then lead to differences in the latency of the focal movement. While such a mechanism is plausible, the work by Anson and Bird (1993) suggests this is unlikely. In their study, finger movements yielded increases in reaction time, while arm movements did not. This observation is counterintuitive to a mechanical explanation given that the fingers have low inertial properties and their movements would not be expected to require time
consuming postural adjustments, whereas the opposite is true of the arms. Thus, a simple mechanical explanation does not appear feasible. A second possibility is that the increase in reaction time reflects task-related differences in central processes, such as motor programming. For example, movement complexity has long been known to influence reaction time (Henry & Rogers, 1960). Complex movements consisting of a number of sequential elements take longer to initiate than movements that consist of only one element. This finding has been replicated repeatedly (e.g., Ketelaars, Garry & Franks, 1997). A number of authors have suggested that bilateral movements might be more complex than unilateral movements due to the greater number of limbs involved, and therefore require more time for movement initiation (Kelso et al., 1979; Marteniuk & MacKenzie, 1980; Swinnen et al., 1995). The implication of this suggestion is that reaction time differences are related to the nature of the task (unilateral vs. bilateral) rather than specific effectors. Again, the results of the study by Anson and Bird (1993) suggest this is not the case as only finger movements yielded increases in reaction time.

1.4. Transcallosal inhibition

One proposal for the bilateral influence on reaction time that is receiving increasing support is that it reflects inhibitory interactions between the motor areas of the cerebral cortex mediated by the corpus callosum (Ohtsuki, 1981a; 1981b; 1994; Taniguchi et al., 2001). According to this transcallosal inhibition hypothesis (TI hypothesis), performing bilateral movements requires the simultaneous activation of the motor areas of the left and right cerebral hemispheres. This activity is accompanied by concurrent activation of callosal pathways that connect the motor areas of one hemisphere with the homologous region in the contralateral hemisphere. While there are several postulated roles for the corpus callosum
(e.g., interhemispheric transfer of motor commands, interhemispheric coordination and interhemispheric transfer of sensory information, see Geffen et al., 1994) one physiological property of callosal activity is interhemispheric inhibition. (Asanuma & Okuda, 1962; Ferbert et al., 1992; Meyer et al., 1995; Meyer & Voss, 2000; Salerno & Georgesco, 1996). Activation of the motor areas in one hemisphere leads to a simultaneous inhibition of activity in the homologous region of the opposite hemisphere via transcallosal projections. When bilateral movements are performed, each hemisphere inhibits the other resulting in a mutual inhibition that leads to reductions in force (Li et al., 2000; Ohtsuki, 1981a; 1994) and increases in reaction time (Ohtsuki, 1981b; Taniguchi et al., 2001). While TI appears to be somewhat detrimental when bilateral movements are performed, it is thought to be functionally important when unilateral movements are required as it minimizes unwanted activation of the contralateral hemisphere (Allison et al., 2000; Geffen et al., 1994; Mayston et al., 1999).

1.4.1. Evidence of callosal inhibition

Direct evidence of callosal inhibition has been obtained from animal studies. Asanuma and Okuda (1962) investigated the effect of intracortical microstimulation of pyramidal tract cells in one hemisphere of cats on the activity of pyramidal tract cells in the opposite hemisphere. They observed that electrical stimulation resulted in excitation of cells in the homologous region of the opposite hemisphere. However, this excitation was restricted to a very small region that was surrounded by a much larger area of inhibition. The observed excitation and inhibition also behaved differently with increasing stimulation intensities. As the stimulation intensity increased, there was an initial increase in the activity within the excitatory area. With further increases, the excitatory activity leveled and eventually became
delayed or absent. The surround inhibition, however, continued to increase and eventually overwhelmed the more restricted region of excitation. Thus, it appears that callosal connections have both an excitatory and inhibitory action, but that the inhibitory action is more widespread.

Evidence from transcranial magnetic stimulation (TMS) studies suggests that the corpus callosum behaves in a similar manner in the human brain. TMS is a technique that uses a powerful magnetic field produced through an encased coil of wire to induce electrical eddy currents in the cerebral cortex. This induced electrical current results in activation of pyramidal neurons, probably trans-synaptically, producing a measurable EMG response in muscles on the contralateral side of the body (Rothwell, 1997). This evoked response has been termed the motor evoked potential, or MEP. Because it is felt that TMS activates cortical output (pyramidal) neurons trans-synaptically rather than directly, the evoked responses are sensitive to changes in intracortical excitation and inhibition. This property of TMS makes it an extremely useful tool for investigating changes in motor cortical involvement in the production of different motor tasks (Rothwell, 1997). Because callosal fibers synapse within the cerebral cortex, TMS can be used to quantify the influence of callosal activity on motor cortical excitation (Ferbert et al., 1992).

Using a paired-pulse technique, Ferbert et al. (1992) were able to demonstrate callosal inhibition in human subjects. In this paradigm, a ‘conditioning’ stimulus is delivered to one hemisphere while a ‘test’ stimulus is delivered to the opposite hemisphere. The conditioning stimulus activates transcallosal fibres and their influence on the opposite hemisphere can be studied by monitoring changes in the amplitude of the MEP evoked by the test stimulus. Ferbert et al. (1992) studied both hand muscles (first dorsal interosseous, FDI) and muscles...
of the upper arm (biceps brachii, BB). For both muscles, when the conditioning stimulus preceded the test stimulus by 6 ms or more, the MEP evoked by the test stimulus was reduced in size. This was observed for both FDI and BB muscles, although the magnitude of the reductions reported were slightly greater for FDI (conditioned responses were reduced by ~ 40%) than BB (conditioned responses reduced by ~ 20%). The researchers also tested the ability of the conditioning stimulus to influence voluntary activation of the opposite motor cortex by having subjects maintain a voluntary isometric contraction. The conditioning stimulus was able to induce a pronounced period of inhibition in FDI, but its influence on BB was more variable. For some subjects, inhibition was readily observed while for others there was no effect. They speculated that this difference between muscle groups might reflect differential involvement of the corticospinal system in the control of the two muscle groups. Distal muscles, especially those of the hand, are highly dependent on the corticospinal system which is necessary for independent control of the fingers (Lemon, 1993). Proximal and truncal muscles, by contrast, receive a greater input from other descending systems, such as the cortico-reticulospinal system (Brinkman & Kuypers, 1973). Ferbert et al. (1992) suggested that transcallosal inhibition may have its greatest effect on corticospinal neurons, thereby having a relatively weaker effect on proximal muscles. This suggests the possibility that tasks involving different muscle groups will be accompanied by different degrees of callosal inhibition, with a greater inhibition associated with distal compared with proximal muscle groups.

Salerno and Georgesco (1996) also used a paired-pulse paradigm to investigate the callosal pathways. They reported that when the interstimulus interval between the conditioning and test stimulus was short (less then 6 ms) the response evoked by the test
stimulus increased in amplitude consistent with transcallosal ‘facilitation’. When the interstimulus interval was lengthened, the amplitude of the test response decreased, consistent with the observations of Ferbert et al. (1992). These different responses might reflect the facilitatory and inhibitory callosal responses observed in animal experiments (Asanuma & Okuda, 1962). Ferbert et al. (1992) also reported a facilitatory response at short latencies but noted that it was ‘capricious’. In addition, the facilitation observed by Salerno & Georgesco (1996) disappeared when unilateral or bilateral voluntary muscle contractions were performed, while inhibition was still observed. In the study by Ferbert et al. (1992) transcallosal inhibition was found to increase with bilateral contractions. That callosal inhibition continues unabated during voluntary contraction has led to speculation that it might have an important role in the production of strictly unilateral movements (Geffen et al., 1994).

The effect of callosal abnormalities on these TMS induced responses has also been investigated (Meyer et al., 1995). In this study, the influence of unilateral TMS on the voluntary activation of ipsilateral hand muscles was in a group of control subjects and in subjects with callosal abnormalities. When the control subjects voluntarily contracted the muscles of one hand, ipsilateral TMS was able to induce a suppression of activity consistent with other studies (Ferbert et al., 1992; Salerno & Georgesco, 1996). In contrast, this suppression was delayed or absent in subjects with callosal abnormalities suggesting that it is mediated through transcallosal pathways. The authors also observed that contraction of the hand muscles ipsilateral to TMS produced a marked facilitation in the MEP evoked in the relaxed hand (contralateral to the TMS). Thus, contraction of the right hand muscles increased the size of the MEP in the left hand when the right hemisphere was stimulated. At
first glance this might appear as evidence for transcallosal facilitation, rather than inhibition. However, this facilitation was observed both in control subjects and in subjects with callosal abnormalities suggesting the excitatory effect was mediated by a spinal mechanism. In addition, Ferbert et al. (1992) noted that when the muscles in both hands were contracted simultaneously, the MEP evoked by the test shock was more inhibited, not less as would be expected if the facilitation were mediated through transcallosal pathways.

Studies of split-brain subjects belie the inhibitory involvement of the corpus callosum in motor tasks. Gazzaniga and Sperry (1966) tested both normal controls and patients [about to undergo a surgical commissurotomy procedure (section of the callosal fibers) to control intractable epilepsy] using a unilateral/bilateral double discrimination task. The task required discrimination between red and green stimuli and light and dark stimuli by pressing keys with the right and left hands, respectively. For both the normal controls and the patients pre-surgery, reaction times were significantly faster for unilateral responses than for bilateral responses. This observation is consistent with many of the previously reported studies (Kelso et al., 1979, 1980; Marteniuk and colleagues, 1980, 1984). Following surgery, however, the difference between unilateral and bilateral responses disappeared owing largely to a reduction of bilateral reaction times with little influence on unilateral reaction time. The authors concluded that sectioning the commissural fibers removed the 'interference' normally present between the hemispheres. As a result, bilateral responses could be performed without interference from the contralateral hemisphere leading to overall faster reaction times.

Zaidel and Sperry (1977) reported similar results with split-brain subjects when they performed a unilateral/bilateral tapping task. Subjects were required to perform rapid
tapping movements involving the fingers or the arms, both under unilateral conditions and bilateral conditions. When normal subjects perform this task, tapping speed is typically reduced with bilateral movements relative to unilateral performance (Wyke, 1971). In contrast to this, the split-brain subjects demonstrated only slight decrements in tapping speed. This suggests that at least part of the slowing during bilateral movements is mediated by interhemispheric interactions through the corpus callosum.

Further support for the transcallosal inhibition hypothesis comes from two recent studies of normal subjects. First, Taniguchi et al. (2001) had subjects perform unilateral and bilateral key press movements in response to visual stimuli. In addition to measuring reaction time, the authors also recorded cortical potentials during the preparatory period and through movement execution. Analysis of the reaction time data revealed a deficit for the right hand when bilateral movements were performed. This deficit was associated with a reduction in the cortical potentials during the period immediately preceding the motor response. It was concluded that the deficits, both for reaction time and cortical potentials, reflected a reduction of the motor command resulting from the action of callosal inhibitory mechanisms active during the bilateral movement. A second study by Meyer and Voss (2000) investigated the influence of TMS evoked transcallosal volleys on reaction times of simple hand movements. Subjects were required to produce a rapid, right-index finger extension in response to an auditory tone. On some of the trials, a TMS stimulus was delivered over the right motor cortex ipsilateral to the responding hand. To ensure activation of the callosal pathways, TMS intensity was set to 1.6 to 2.1 times the intensity needed to evoke MEPs in contralateral hand muscles. TMS delivered 40 ms to 70 ms following the auditory tone produced a clear delay in reaction time relative to trials on which no TMS was
delivered. They concluded that activation of the callosal projections resulted in an inhibition of the contralateral motor cortex leading to a delay in reaction time.

Clinical and developmental studies provide additional evidence for the inhibitory role of the corpus callosum. An occasional occurrence following surgical section or insult of the corpus callosum is a conspicuous increase in associated (mirror) movements and the development of an ‘alien hand’. Geschwind et al. (1995) report the case of a 68 year old woman who suffered a stroke affecting the body of the corpus callosum while in the hospital for heart bypass surgery. One of the early symptoms of the stroke was that her left-hand began to act completely of its own accord. She reported that it would attempt to choke her, would throw objects from her food tray onto the floor and would interfere with the actions of her right hand, such as unbuttoning the shirt that her right hand had just done up. She reported that it felt as if her left hand was being controlled “from the moon”. In addition to this alien hand sign, she also displayed mirror movements. She was unable to perform tasks with her left hand without concomitant mirror activity involving her right hand, something which she was completely unaware of until it was pointed out to her.

Mirror movements are also very common in children up to approximately 10-12 years of age and are thought to be a reflection of the immaturity of callosal pathways. A recent study (Mayston et al., 1999) reported the presence of mirror movement and EMG activity in the hand muscles during voluntary intended unilateral hand movements of the youngest children studied (age range = 4 to 11 years). In the older children, mirror activity was still observable in the recorded EMG although overt associated limb movements were no longer visible. Mirror EMG activity was rarely visible in adults. The authors also reported that a paired TMS paradigm, similar to that of Ferbert et al. (1992), could readily demonstrate
transcallosal inhibition in adults, but not in children supporting the contention that
immaturity of callosal pathways contributes to the expression of mirror movements. As the
corpus callosum develops, the incidence of mirror activity is reduced and pure unilateral
movements are more readily executed.

While mirror movements are not as common in adults as in children, they are
nonetheless observable on occasion. Leocani et al. (2000) reported that eight of nine subjects
displayed mirror movements during intended unilateral finger movements. Interestingly,
mirror movements were more common when non-dominant hand (left) movements were
performed. The authors suggested that this might reflect stronger transcallosal inhibition
from the dominant to the non-dominant hemisphere than vice-versa. This suggestion is
supported by a TMS study reporting greater inhibition from the left hemisphere to the right
than from the right hemisphere to the left in right handed subjects (Netz et al., 1995).

1.5. A study of the influence of spatial precision on unilateral and bilateral reaction time

On the basis of the preceding evidence, there seems to be reasonable support for a
transcallosal inhibitory mechanism mediating the increase in reaction time during bilateral
movements. However, not all studies investigating bilateral movements report increases in
reaction time. Recall that in the study by Anson and Bird (1993) reaction time increased
when bilateral finger extension movements were required. In addition to finger extension
movements, the authors also tested elbow flexion movements. Unlike finger extension, no
increase in reaction time was observed when the elbow flexion task was performed. In
another study Swinnen et al. (1995) reported a similar failure for reaction time to increase
when elbow flexion movements were performed. In this study, subjects were required to
perform limb movements involving one, two, three or four joints simultaneously. Single-
joint movements required either an elbow flexion or a leg extension movement. Two joint movements required simultaneous bilateral elbow flexion movements or leg extension movements. Three joint movements involved either both arms and one leg, or one arm and both legs, while four joint movements involved all four limbs simultaneously. While reaction times increased when the task involved three or four limbs, bilateral movements did not yield any significant increase in reaction time. A third study requiring bilateral elbow flexion movements (Taniguchi, Nakamura & Oshima, 1977) reported relatively small differences between unilateral and bilateral movement conditions (~2 ms), although this difference was statistically significant. If transcallosal inhibition is responsible for the increase in reaction time when bilateral movements are performed, why wasn’t there an increase in these studies?

The experiments of Kelso et al. (1979, 1983) and Marteniuk and colleagues (1980, 1984) all reported increases in reaction time for tasks requiring arm movements, therefore the different findings cannot be attributed to differences between effectors. A potentially important factor differentiating these experiments, however, was the requirement for spatial precision. The task required by Anson and Bird (1993), Swinnen et al. (1995) and Taniguchi et al. (1977) did not place any emphasis on movement precision, while the experiments by Kelso et al. (1979, 1983), Marteniuk and others (1980, 1984), Stelmach and Worringham (1988) and Fowler et al. (1991) did. It might be, therefore, that the requirement for movement precision influences transcallosal inhibition and therefore determines whether reaction time will increase when bilateral movements are performed.

In a recent study (Garry & Franks, 2000), we tested the hypothesis that movement accuracy would influence reaction time when bilateral movements were required. This
argument was based in part on a study reporting increased cortical activity when performing precise movements. Schieppati et al. (1996) observed that for both distal and proximal muscles, cortical excitability increased when precise control was required. They suggested there might be a group of cortical cells responsible for controlling precision and that the involvement of these cells is based on a selective mechanism dependent on task requirements. It might be expected, therefore, that movements required to be spatially accurate would involve a greater, or different, degree of cortical excitability than movements for which precision is unimportant. If transcallosal inhibition is dependent on cortical excitability, increasing the demands for movement precision would be expected to have a concurrent influence on callosal inhibition. As a result, the greater the required precision, the longer the reaction time during bilateral movements.

To test this hypothesis we had subjects perform unilateral and bilateral elbow flexion movements requiring two different levels of movement precision (Garry & Franks, 2000). It was hypothesized that reaction times for unilateral and bilateral movements would not differ when the spatial constraints of the task were very low, but bilateral reaction time would exceed unilateral reaction time when the spatial constraints were high. To simplify the task and remove the potential confound of having to monitor the movements of both arms simultaneously, spatial precision was emphasized for only one arm (the "aiming" arm) during the bilateral task. The other arm (the "mirroring" arm) simply performed a simultaneous, symmetrical flexion movement with no emphasis on movement precision.

1.5.1. Procedures

Subjects were required to make unilateral and bilateral elbow flexion movements of 45° as quickly and accurately as possible. The arms were positioned on identical manipulanda
that limited movements to the horizontal plane. Moving the arm caused a 'response cursor' (1 mm dot) displayed on an oscilloscope screen to move between a start location and a target region. During bilateral trials the response cursor was displayed for only one arm—the aiming arm—and no position information was provided for the contralateral arm. When the left arm was the aiming arm, flexing the elbow caused the response cursor to move from the left side of the screen toward the target positioned on the right side of the screen. This mapping was reversed when the right hand controlled the cursor. In this way, cursor movement and arm movement were congruent regardless of which hand was the aiming hand. Each participant performed two blocks of 10 trials in each of four movement conditions: unilateral left, unilateral right, and two bilateral movements, left-arm aiming and right-arm aiming. In one block, subjects performed the movements to small targets (1.5°), while in the other block movements were made to large targets (12.0°). The order of the blocks was counterbalanced across subjects. Figure 1.1 presents a schematic of the different movement conditions and the visual display.

1.5.2. Results

It was our expectation that reaction time during bilateral movements would depend on the level of accuracy required and would exceed unilateral reaction time only when the required accuracy was high (1.5° target), but not when it was low (12.0° target). Contrary to this expectation, however, target size, neither as a main effect nor interaction, had any significant influence on reaction time. This was not simply due to a lack of accommodation to the different target sizes as both peak velocity and average velocity were significantly reduced when movements were made to the small target compared to movements made to the large target (see figure 1.2). This reduction in movement velocity to the small target is
Figure 1.1. Schematic of experimental setup. The black dot is the response cursor controlled by the subject through flexion of the aiming arm (filled). The two vertical lines on the oscilloscope denote the target region. Position of the mirroring arm (open) is not provided. Note that when the left arm is the aiming arm, the positions of the response cursor and the target region are reversed.
Figure 1.2. Mean peak velocity and average velocity of elbow flexion to the large (12.0°) and small (1.5°) targets. Consistent with Fitts’ (1954) Law, velocity was reduced when executing movements to the small target indicating that the participants were compensating for the different target sizes.
consistent with Fitts' Law (1954) which notes that in order to increase movement accuracy, the speed of the movement must be reduced. Thus, even though subjects were clearly compensating for changes in target size by reducing movement velocity, this compensation was not reflected in the reaction time measure.

On the basis of this result, one might be inclined to argue that movement precision does not play an important role in the bilateral-unilateral reaction time deficit. However, we felt this conclusion was unwarranted in light of a significant hand by condition interaction for premotor time (PRT) (see figure 1.3). An analysis of the interaction revealed that when bilateral movements in which the right arm was aiming were performed, PRT differed little between unilateral and bilateral conditions. In contrast, PRT of both arms increased when the left arm was the aiming arm. This suggests that it is not movement precision, or even movement type (unilateral or bilateral) that influences reaction time, but the hand on which precision demands are placed. What is the mechanism responsible for this particular pattern of results? There are several potential mechanisms which might explain these findings.

### 1.5.3. Possible explanations

One possibility is that there are biomechanical differences between the movement conditions requiring different anticipatory postural strategies. If the postural strategy for one movement condition is more time consuming than those required for the other movement conditions, the reaction time of the focal movement might be delayed. This seems unlikely, however, as the left-arm aiming (BL) and right-arm aiming (BR) bilateral conditions differed only in terms of the hand that controlled the cursor. Any biomechanical differences between the unilateral and bilateral tasks would be expected to affect both bilateral movements in a similar manner. As this was not the case, this explanation is unlikely. Another possibility is
Figure 1.3. Premotor reaction time (PRT) for the left and right hands for the unimanual (UNI) and bimanual movement conditions. The BI condition indicates the bimanual condition in which the hand was the aiming hand, while the MIR condition indicates that the hand was mirroring. Thus, left hand BI and right hand MIR shows the performance of both hands when the left hand was aiming. Right hand BI and left hand MIR shows performance when the right hand was aiming. Note that reaction times increased for both arms when the left arm was required to execute spatially precise movements (left arm BI, right arm MIR).
that the tendency for the arms to become synchronized in their reaction times when bilateral movements are performed (Di Stefano et al., 1980; Kelso et al., 1979) would demand that the intrinsically faster arm delay initiation to match that of the slower arm. This explanation is also doubtful as there were no overall differences in reaction time between the left and right hands, and there were no differences between the hands at any of the movement conditions. In addition, as with a biomechanical explanation, such an effect would be expected to influence both bilateral movement conditions. Further, this should impact only the arm with the intrinsically faster reaction time, while in this experiment both arms increased their reaction times in the BL movement condition. Finally, it might be argued that for right handed subjects, movements requiring precision with the left arm will be initiated more slowly due to intrinsic differences in the ability of the dominant and non-dominant arms to execute precise movements. While it is true that movement time is often greater for the left arm, it is also common for left arm movements to be initiated more quickly than the right arm movements. This left-hand reaction time advantage has been attributed to the to the right hemisphere's putative greater spatial processing abilities (Bradshaw et al., 1990; Elliott et al., 1993; Hodges et al., 1997; Roy, Kalbfleisch & Elliott, 1994). What, then, is the reason for the increased reaction time in the BL movement condition, and why did reaction time not increase when the right hand was performing the aiming movement?

1.6. Ipsilateral control

It was interesting to us that in the study by Anson and Bird (1993), bilateral reaction time exceeded unilateral reaction time for distal muscles, but not for proximal muscles. An important distinction between these muscle groups is that the distal muscles of the hand are controlled almost exclusively by the contralateral hemisphere (Haaxma & Kuypers, 1975)
while proximal muscles can be controlled both from the contralateral hemisphere, as well as from the ipsilateral hemisphere (Brinkman & Kuypers, 1973; Jakobson et al., 1994). Given that the movements in our experiment (Garry & Franks, 2000) involved proximal muscles, it seems possible that the different effects on reaction time of the BL and BR movement conditions could be accounted for by differences in the hemispheric control of the arms in the two conditions. Maintaining the assumption that transcallosal inhibition is responsible for the observed reaction time increases associated with bilateral movements, the results of our study imply the presence of transcallosal inhibition during the BL movements, but not during the BR movements. The failure for reaction time to increase in the BR condition could occur if both the right and left arm movements were initiated from a single hemisphere. This would eliminate interhemispheric interactions during the initiation phase of the movement and effectively abolish the transcallosal influence on reaction time. By contrast, if both hemispheres participate in the BL movement condition, transcallosal inhibition would lead to an associated increase in reaction time. A schematic of this model is presented in figure 1.4.

1.6.1. Evidence for ipsilateral control

What evidence is there to support the possibility of ipsilateral control? In what is now a classic experiment, Brinkman and Kuypers (1973) observed that monkeys, following a surgical section of the corpus callosum, were able to perform accurate reaching movements to food morsels presented to either the ipsilateral or contralateral visual field. Because of the organization of the visual pathways, objects presented in a given visual field are perceived by the contralateral cerebral hemisphere. Hence, when food was presented in the monkey's right visual field it was perceived by the left hemisphere. Because the two hemispheres
Figure 1.4. Schematic representation of the proposed model of control. (a) Unilateral right-hand movement, (b) unilateral left-hand movement, (c) bilateral left-hand aiming, and (d) bilateral right-hand aiming. The gray, double-headed arrow in (c) indicates the presence of transcallosal inhibition.
could not communicate with one another (at least not through direct transcallosal pathways), a successful reach by the left hand (ipsilateral to the perceiving hemisphere) was interpreted as control of that arm through ipsilateral pathways. By contrast, the fingers and hands behaved as if ‘blind’ under this condition. There was no anticipatory grip formation and the fingers appeared to explore the board on which the food was contained. It was not until contact with the food was made that the monkey was able to perform an appropriate grasping action. The conclusion was that either hemisphere could effectively control the proximal muscles of the arm involved in the reach component. However, efficient control of the distal muscles of the hand can only be obtained through contralateral control.

Similar observations have been obtained with human subjects as well. Jakobson et al. (1994) found that both normal and acallosal subjects could successfully reach to objects situated in the visual field contralateral to the reaching arm which meant the arm was under control of the ipsilateral hemisphere. Consistent with Brinkman and Kuypers (1973), the authors interpreted this result as evidence of ipsilateral control of the proximal muscles involved in the reach component. It was noted, however, that reaches under ipsilateral hemispheric control took significantly longer to complete than reaches under contralateral hemispheric control, and that this difference was especially large for the acallosal subjects. They concluded that while it is possible to control the proximal muscles of the arms through ipsilateral pathways, such control comes at the cost of a reduced efficiency of movement—at least when the movement is intended to be both fast and accurate. Thus, when both contralateral and ipsilateral pathways are available, the requirement to execute a fast and

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1 Someone who is acallosal has a congenital absence of the corpus callosum.
accurate movement should restrict control to the contralateral hemisphere (Todor et al., 1982).

Further evidence of ipsilateral control is obtained from crossed-uncrossed paradigms (Aglioti et al., 1993; Di Stefano et al., 1980). In these studies, a simple unilateral or bilateral movement is initiated in response to a lateralized visual stimulus. The stimulus is considered 'crossed' if one hemisphere perceives the stimulus and the other hemisphere controls the motor response. The stimulus is uncrossed if the hemisphere that controls the response is the same hemisphere to which the stimulus is directed. For crossed responses, information about the stimulus must be transferred from the perceiving hemisphere to the responding hemisphere prior to response initiation. No crossing is required for uncrossed responses. The time needed for the stimulus information to cross hemispheres is reflected in reaction time and is termed the interhemispheric transfer time (Berlucchi et al., 1994).

For unilateral movements, responses to crossed stimuli take longer to initiate than responses to uncrossed stimuli, both for distal and proximal muscles. The results are somewhat different, however, when bilateral responses are performed. For distal muscles, crossed reaction time still exceeds uncrossed reaction time, but for proximal muscles the difference is completely absent (Di Stefano et al., 1980). This is the case both for control subjects as well as subjects with callosal abnormalities. This is an important observation as interhemispheric transfer times in these individuals can be as much as 10X greater than for control subjects (Aglioti et al., 1993). The absence of a difference between crossed and uncrossed responses during bilateral proximal movements has been interpreted as evidence that an interhemispheric transfer is not required and that the movements of both arms are
initiated via the same hemisphere through a bilaterally distributed motor system (Aglioti et al., 1993; Berlucchi et al., 1994; Di Stefano et al., 1980).

Another line of evidence pointing to the involvement of ipsilateral pathways comes from studies of individuals with unilateral brain lesions. Colebatch and Gandevia (1989) tested the strength of upper-limb muscles on both sides of the body in control subjects and in subjects with unilateral cerebral lesions. It was observed that the patient group was substantially weaker on the side of the body contralateral to the damaged hemisphere. However, the extent of weakness was not symmetrical for all muscle groups. Distal muscles, especially those of the hand, were most severely affected. Proximal muscles, in particular the shoulder, were observed to have a relative sparing of strength. In addition, the muscles on the 'unaffected' side, ipsilateral to the damaged hemisphere, also showed reduced strength. In this case, however, proximal muscles were the most severely affected while distal muscles were least affected. The authors concluded that these different patterns of weakness on the affected and unaffected sides could be accounted for by differing contributions of ipsilateral projections to distal and proximal limb muscles. Because the muscles of the hand are heavily dependent on contralateral pathways, the hand muscles will be profoundly affected by a lesion of the contralateral hemisphere and strength of the ipsilateral hand will be relatively spared. In contrast, the shoulder and upper arm muscles contralateral to the lesioned hemisphere will retain a greater percentage of strength due to the involvement of the unaffected hemisphere. The muscles ipsilateral to the affected hemisphere will lose some strength as a result of disruption of the ipsilateral projections.
1.6.2. Asymmetries of ipsilateral control

In the context of our task (Garry & Franks, 2000), the work of Jakobson et al. (1994) suggests that the aiming arm will always be controlled by the contralateral hemisphere, due to the requirement to perform a precise movement. This, therefore, makes up an important first assumption of the model: When the movement requires precision, control will always derive from the contralateral hemisphere. The mirroring arm, by contrast, could be controlled through ipsilateral pathways as movement precision is not emphasized for this arm and efficient control is therefore not as important. However, we argue that the ability to control the arms from the ipsilateral hemisphere is not equal across the right and left sides. The result is that the right arm is biased toward contralateral control regardless of the movement condition while the left arm can come under ipsilateral control with greater efficiency. This leads to the second assumption of this model: Where the task allows for ipsilateral control, there will be a stronger bias toward left arm ipsilateral control than right arm ipsilateral control. The result is that when a movement requires accuracy only from the right arm, both arms can be controlled from a single (left) hemisphere. In contrast, when the left arm is required to move with precision it will come under control of the right hemisphere (in order to execute the movement accurately) while the right arm will continue to be controlled by the left hemisphere. In this situation, both hemispheres will participate in movement initiation leading to a transcaldosal inhibitory influence on reaction time.

The studies by Brinkman and Kuypers (1973) and Jakobson et al. (1994) provide support for the first assumption. What evidence is there for the second assumption that the motor system is biased in favour of left-arm ipsilateral control? One prediction from this assumption would be a tendency for the right-arm to be dominant in movement. Because the
right arm is more likely to be controlled through efficient contralateral pathways, the movements of the right arm might be expected to exhibit a greater degree of skill than movements of the left arm. Certainly for the approximately 90% of the population that is right-hand dominant (Calvin, 1983), this appears to be the case. However, observing that people with a preference toward using their right hand display more skill with that hand is not an indication that the greater dexterity arises from differences in how the motor system controls the arms. It might just as easily reflect the greater opportunities for the right hand to develop proficiency through greater use. Another prediction would be that during bilateral movements, the right hand would be more likely to assume the dominant role. In this regard, Peters (1994) points out the following aspects of naturally occurring bimanual coordinated movements. First, the primary goal of the task is commonly realized through the movements of the right arm. Second, coordination often involves a precise timing of the onset of movement of the right arm, with respect to the more postural role of the left. Third, the right arm will typically perform those aspects of the movement that require precise adjustment and fine control of speed. And fourth, the right arm typically receives a continuous allocation of attention while the left arm receives attention more intermittently. These aspects of bimanual movements emphasize a strong bias toward executing precise movements with the right arm consistent with contralateral control. The less prominent role of the left arm could be realized through ipsilateral pathways.

Additional evidence of the greater reliance of the right arm on contralateral control and the greater involvement of ipsilateral control for the left arm comes from studies of individuals who have suffered unilateral stroke. Wyke (1967) observed that for subjects with unilateral cerebral lesions, left and right arm performance of rapid movements was
differentially influenced by the hemisphere in which the lesion was located. While right hemisphere lesions resulted in the slowing of movements of the left hand relative to control subjects, left hemisphere lesions were associated with a slowing of both hands. From this evidence, Wyke (1967) suggested that the right hemisphere is involved only in left hand movements, while the left hemisphere contributes to both right and left hand movements. It was further argued that the right hemisphere might be unable to exert ipsilateral control over the right hand, or that such control is less efficient than ipsilateral control arising from the left hemisphere. Similar bilateral impairments with left-hemisphere damage were observed for tasks involving precise movements (Wyke, 1968).

Studies of arm gestures during speaking are also consistent with a predominance of contralateral control for the right arm. Kimura and Humphrys (1981) recorded movements of the right and left arms of subjects while they were speaking. For both bilateral and unilateral gestures, the right arm underwent more movement oscillations than the left arm suggesting that it was governed by the contralateral (left) ‘speaking’ hemisphere. While it was concluded that the left-arm’s movements were similarly controlled by the left-hemisphere due to the tight temporal coupling of the two arms, the study did not allow a determination of whether the control was exerted through ipsilateral pathways or via communication through callosal pathways.

Imaging studies have also provided evidence consistent with hemispheric asymmetries in the control of the arms. Kawashima et al. (1993) observed that when (right-handed) subjects performed a unilateral sequential finger/thumb opposition task with the right hand, regional cerebral blood flow (rCBF) increased only in the left motor cortex. When they performed the same task with the left hand, however, there were significant rCBF increases
in both the right and left motor cortices. It was suggested that left hand movements are more complex than right hand movements and therefore require ipsilateral motor cortex activity "when it is necessary for a specific movement" (p. 38). Whether the ipsilateral activity during left-hand movements exerts an influence through ipsilateral descending pathways or through cortico-cortical (transcallosal) connections was unclear.

A recent TMS study (Caramia et al., 2000) provides more direct evidence of a bias toward left-hemisphere ipsilateral control. In this study, TMS was used to investigate the involvement of ipsilateral projections in the recovery of the affected arm following unilateral stroke. During stimulation of the unaffected hemisphere, MEPs could be evoked in the muscles of the recovered hand of the patients suggesting that ipsilateral pathways play an important role in functional recovery. In addition to the patient group, a group of normal control subjects was also tested using the same paradigm. Out of twenty subjects, ipsilateral MEPs were observed in eight. Of greatest interest was the fact that ipsilateral MEPs were only observed with stimulation of the left hemisphere.

In addition to a bias toward ipsilateral efferent involvement from the left-hemisphere, there is also evidence that ipsilateral afferent pathways are more prominent for the left than right sides. Geffen, Nilsson, Quinn and Teng (1985) tested finger localization in a group of commissurotomy patients. They reported that while correct responses were higher when subjects responded with the stimulated hand, cross-localization (responding with the opposite hand) was significantly more accurate when responses were performed with the right hand compared with responses performed with the left hand. The authors suggested that tactile information from the left hand was available to the ipsilateral left-hemisphere, thereby allowing correct right-hand responses to be performed in some cases. A similar finding was
reported by Papagno and Marile (1995) for a woman who suffered lesions of the corpus callosum and the right frontal lobe. When she could not see her left hand she was unable to replicate postures performed with her right hand, however, she could successfully replicate left-hand postures with her right hand suggesting that sensory feedback from the left hand was available to the left hemisphere.

On the basis of these findings, it appears plausible that bilateral right-arm aiming and left-arm aiming movements could differ in terms of hemispheric control (and therefore transcallosal inhibition), and that this difference is responsible for the longer reaction times observed for the left-arm aiming movements. The model proposed here contains two important assumptions that will be addressed using different experimental paradigms.

**Assumption 1:** the aiming arm, regardless of whether it is the left or the right, is always controlled by the contralateral hemisphere. **Assumption 2:** while the non-task (mirroring) arm can be controlled through ipsilateral pathways, such control will predominantly occur for the left hand as a result of hemispheric asymmetries in the efficiency of ipsilateral pathways.

It is important to note however, that this assumption of a bias toward left-hemisphere ipsilateral control does not exclude the possibility that, under some conditions, the right arm might be controlled by the right hemisphere. There is some evidence to suggest that, with lateralized visual stimuli at least, ipsilateral control is available to both arms (Aglioti et al., 1993; Di Stefano et al., 1980). However, the assumption here is that under most conditions, control of the left arm through ipsilateral pathways is more readily achieved than similar control of the right arm.
1.6.3. The present experiments

Three experiments will be summarized in this thesis. **Experiment 1** was designed to assess the first assumption that the aiming arm is controlled by the contralateral hemisphere. This was done using a crossed-uncrossed differences paradigm similar to that used by Aglioti et al. (1993) and Di Stefano et al. (1980). **Experiment 2** was designed to determine whether the pattern of reaction times observed in our earlier study (Garry & Franks, 2000) involving proximal arm movements could also be demonstrated for more distal muscles. While the bulk of the literature suggests that distal muscles are controlled by the contralateral hemisphere (Brinkman & Kuypers, 1973; Haaxma & Kuypers, 1975; Jakobson et al., 1994), recent evidence from TMS studies suggests that certain distal muscles are accessible through ipsilateral pathways (Wasserman et al., 1991, 1994; Ziemann et al., 1999). If this pathway are sufficiently powerful to initiate a movement than results similar to our earlier study (Garry & Franks, 2000) can be expected. **Experiment 3** was designed to test directly the hemispheric control of the arms using a combined reaction time TMS paradigm. Because TMS can influence the motor pathways involved in the control of the arms, this paradigm provided an opportunity to test directly the hemispheric control of the left and right arms during bilateral movements.
1.7. Statement of ethics

All the experiments that follow were conducted in accordance with the ethical guidelines of the University of British Columbia.
2. Experiment 1: Hemispheric control of the aiming hand in unilateral and bilateral movements: A crossed-uncrossed stimulus study.

2.1. Introduction

While there are several assumptions that constitute the present model, one of substantial importance is that the instruction to execute spatially precise movements restricts control of the aiming arm to the contralateral hemisphere. This assumption is based largely on the evidence of Jakobson et al. (1994) who showed that for acallosal subjects, the time required to complete the reach component of a prehension movement was substantially increased when reaches were executed under the control of the ipsilateral hemisphere. Their conclusion was that while the ipsilateral hemisphere is able to control arm movement, it does so with reduced efficiency relative to the contralateral hemisphere leading to decrements in overall movement time. Thus, under conditions where both ipsilateral and contralateral control is available, the requirements of the task might determine which pathway is used (Todor et al., 1982). In the context of the present experiments, the requirement to perform rapid, spatially precise movements is assumed to be the determining factor. However, given the task required by the subjects in the experiment by Jakobson et al. (1994) it is possible that the observed decrement in performance might not be as substantial as the authors suggest.

The task used by Jakobson et al. (1994) required subjects to perform reaches unilaterally. Some have suggested that the ipsilateral pathways, at least for proximal muscles, are not efficiently accessed when performing unilateral movements (Aglioti et al., 1993; Berlucchi et al., 1994). Thus, the observed deficiency of ipsilateral control might derive from an inability to fully access the ipsilateral pathways. The requirement to execute bilateral movements might improve access to these pathways enabling a greater efficiency of ipsilateral control.
If this is correct, the influence of movement condition on reaction time in our earlier study (Garry & Franks, 2000) might reflect differences in the hemispheric control of the ‘aiming’ arm, rather than differential control of the mirroring arm. A second source of reduced efficiency relates to the requirement for simultaneous distal control in the task used by Jakobson et al. (1994). The prehension task used in that experiment might have influenced proximal control even if the proximal arm muscles could be effectively controlled through ipsilateral pathways. Because the ultimate goal of the task was to successfully grasp an object in the hand, performance may have been impaired by the poor ipsilateral control of the hand muscles (Brinkman & Kuypers, 1973). While studies suggest the transport and grasp components of a prehension movement are relatively independent (Jeannerod, 1988) these studies have not attempted to manipulate the hemispheric control of these phases. It is possible that under such conditions deficiencies in the grasp component might have a greater impact on the performance of the reach component. Therefore, the purpose of experiment 1 was to assess whether the requirement for spatial precision when performing bilateral movements is sufficient to restrict control of the aiming hand to the contralateral hemisphere.

### 2.1.1. The crossed-uncrossed paradigm

When individuals execute speeded responses to lateralized visual stimuli, those responses are initiated more quickly when the stimuli are presented ipsilateral to the responding limb (uncrossed) than when they are presented contralateral to the responding limb (crossed) (Berlucchi et al., 1994; Marzi, Bisiacchi & Nicoletti, 1991; Poffenberger, 1912). For responses involving the distal muscles of the upper extremities, the difference in reaction time is approximately 3-4 ms and is referred to as the crossed-uncrossed difference, or CUD (Marzi et al., 1991). When such tasks are performed by individuals with callosal
abnormalities, such as callosal agenesis or callosotomy, CUDs are substantially increased—in some cases exceeding 60 ms (Aglioti et al., 1993). Based on these findings, the canonical interpretation is that the CUD represents the time required for interhemispheric transfer of visuomotor information from the perceiving hemisphere to the hemisphere controlling the motor response.

For tasks involving the hands and fingers, control is predominantly via the contralateral hemisphere through crossed pathways (Brinkman & Kuypers, 1973). This neuroanatomical crossing is also present in the visual system such that visual stimuli isolated to one visual hemifield are perceived by the opposite cerebral hemisphere. As an example, consider an individual who must perform rapid, right-hand responses to lateralized visual stimuli. A stimulus presented to the right visual field will be perceived by the left hemisphere which in-turn controls the responses of the right hand. In this uncrossed condition, both visual perception and response organization are carried out within the same hemisphere. This is illustrated in figure 2.1a. The result is rapid visuomotor integration and correspondingly fast reaction times. In the crossed condition, the stimulus is presented to the left visual field, with perception taking place in the right hemisphere. Because the task requires a right-hand response, information about the stimulus must be transferred to the left hemisphere controlling the motor response. This is illustrated in figure 2.1b. In healthy individuals, this transfer is mediated by the corpus callosum and requires an additional 3-4 ms over within hemisphere processing (Marzi et al., 1991). In individuals with callosal abnormalities, interhemispheric transfer is mediated by longer and more slowly conducting extracallosal pathways, increasing the time required for visuomotor integration (Aglioti et al., 1993; Berlucchi, 1994; Milner, Jeeves, Silver, Lines & Wilson, 1985).
Figure 2.1. Examples of (a) uncrossed and (b) crossed conditions relative to the right hand. The dotted line from the stimulus (light) indicates the hemisphere that will perceive the stimulus. The gray arrow from the right hemisphere to the left hemisphere represents interhemispheric transfer.
2.1.2. **Defining crossed and uncrossed conditions**

When discussing the terms crossed and uncrossed, it is important to note that they can have both a spatial and a neuroanatomical reference. In spatial terms, crossed and uncrossed refer to the relative hemispatial position of the responding limb and the visual stimulus. Keeping with the right-hand response example, an uncrossed condition will be obtained when the hand is in right hemispace (i.e., on the right side of body midline) and the visual stimulus is presented to the right visual field (ipsilateral hemispace). The crossed condition will be obtained when the stimulus is presented to the left visual field (contralateral hemispace). These are illustrated in figures 2.2a and 2.2b. If the right-hand is then repositioned in left hemispace (i.e., on the left side of body midline), the crossed and uncrossed conditions become reversed. Here, the uncrossed condition will be obtained with left visual field stimuli (figure 2.2d) while the crossed condition will involve right visual field stimuli (figure 2.2c). While the hemispatial relationship of the responding limb and visual stimulus is known to influence reaction time in choice-reaction time situations (the spatial compatibility effect), it does not affect CUDs in simple reaction time situations (Di Stefano, 1980; Milner et al., 1985). Movements of the right hand are initiated more quickly to a right visual field stimulus than to a left visual field stimulus regardless of the hemispace in which the hand acts. The reason for this is readily apparent when the terms crossed and uncrossed are considered in neuroanatomical terms.

Neuroanatomically, crossed and uncrossed refer to conditions requiring between hemisphere and within hemisphere processing, respectively. When the visual stimulus is presented to the same hemisphere that controls the motor response a neuroanatomically uncrossed condition is obtained. Because the right hand is controlled (predominantly) by the
Figure 2.2. Examples of movements that yield different crossed and uncrossed conditions, both spatially and neuroanatomically. The right (black) hand is the responding hand in each example and is always controlled by the left hemisphere. In (a) and (b) the hands are crossed over the midline. (a) uncrossed both spatially and neuroanatomically, (b) crossed, both spatially and neuroanatomically, (c) spatially crossed, and neuroanatomically uncrossed, and (d) spatially uncrossed, and neuroanatomically crossed.
left hemisphere, this will occur when a stimulus is presented to the right visual field (figures 2.2a and 2.2c). When the stimulus is presented to the left visual field, the right hemisphere perceives the stimulus resulting in a crossed condition (figures 2.2b and 2.2d). Before the response can be initiated, the visual information must be transferred to the responding hemisphere. It is therefore apparent that tasks involving spatially crossed (uncrossed) responses and stimuli do not always produce a neuroanatomically crossed (uncrossed) condition. Recognition of this has allowed researchers to conclude that under certain situations neuroanatomical crossing is not required even though the spatial relationship between stimulus and effector would appear to precipitate such crossing (Berlucchi et al., 1994; Di Stefano et al., 1980; Iacoboni & Zaidel, 1999).

2.1.3. Differences between distal and proximal control

When distal responses are performed, a visual stimulus presented to the hemifield contralateral the responding limb (when the hands are held uncrossed) is always associated with a neuroanatomically crossed condition. This is the case whether unilateral or bilateral responses are performed (Aglioti et al., 1993; Berlucchi et al., 1994; Di Stefano et al., 1980). The situation is the same for unilateral proximal responses. However, this does not appear to be the case when bilateral proximal responses are performed. For these movements the reaction time differences between crossed and uncrossed responses is essentially zero, both in healthy individuals as well as those with callosal abnormalities (Aglioti et al., 1993; Di Stefano et al., 1980) indicating that a neuroanatomically crossed condition does not occur. Regardless of the position of the stimulus, bilateral proximal responses require only within hemisphere processing. This is because proximal, bilateral movements gain access to bilaterally distributed motor pathways not available when unilateral movements are
performed (Berlucchi et al., 1994). As a result, the movements of both arms can be initiated by either hemisphere—the determining factor being the hemisphere receiving the visual stimulus (Di Stefano et al., 1980). This is illustrated in figure 2.3.

Aglioti et al. (1993) suggested that a lateralized stimulus preferentially elicits responses via these bilateral pathways. This makes the side of stimulus presentation the critical factor in the hemispheric control of the arms. However, the assumption of the present experiment is that the requirement for spatial precision determines the hemispheric control of the aiming arm. If this is correct, the aiming arm should always be controlled by the contralateral hemisphere, even for bilateral tasks which provide access to bilaterally distributed pathways. Hence, the aiming arm should respond more quickly to uncrossed stimuli regardless of whether the movement is initiated unilaterally or bilaterally. For this task, then, the mirroring hand is essentially an independent variable manipulated to provide access to the putative bilaterally distributed pathways. If, under both unilateral and bilateral task conditions, the aiming arm is controlled by the contralateral hemisphere, an ANOVA performed on reaction time should reveal a main effect of stimulus position (crossed, uncrossed) with no interaction between stimulus position and movement condition (unilateral, bilateral). However, if the aiming arm can be controlled effectively by either hemisphere in the bilateral movement condition, the position of the stimulus will determine the hemisphere controlling the aiming arm resulting in a significant interaction between stimulus position and movement condition. In this case, movements will be initiated more quickly in response to uncrossed stimuli only during unilateral movements and the advantage for uncrossed responses will be absent when bilateral movements are executed.
Figure 2.3. Control of bilateral movements in response to a visual stimulus in the right visual field. (a) Distal muscles require an interhemispheric transfer to initiate the movement of the left hand. (b) For proximal arm movements, both the left and right arm movements can be initiated simultaneously from the left-hemisphere without requiring interhemispheric transfer.
2.2. Methods

2.2.1. Subjects

Twelve subjects (7 female, 5 male aged 18 – 52 years) gave informed consent prior to participating in the study. All were right-handed according to the Edinburgh Inventory (Oldfield, 1971). All subjects were free of neurological and muscular disorders and had normal or corrected to normal vision.

2.2.2. Apparatus

The right and left forearms of each subject were positioned on identical manipulanda with the elbow joints collinear with the axis of rotation. The hands rested palm down on metal plates fixed to the distal end of the manipulanda with the middle finger positioned between two metal pins. Velcro straps were tightened across the hands and the forearms to restrict arm movements to rotations about the elbow joint in the horizontal plane and reduce the need for tonic muscle activation that would be necessary if one were to grip a handle.

Angular displacement data were obtained from identical optical encoders (Dynapar E20-2500-130) attached to the shafts of the manipulanda. Angular velocity data were obtained by low-pass filtering the displacement data (Butterworth zero-phase shift, cutoff 20 Hz) and differentiating using the finite differences method. All kinematic data were sampled at 1000 Hz. Electromyographic (EMG) activity from the biceps brachii (long head) and the lateral head of the triceps muscles of each arm were recorded using differential Ag/AgCl surface electrodes (8-mm-diameter, spaced 2 cm apart). The signal was amplified (x2000-x20000) using a multichannel EMG amplifier (model 544, Therapeutics Unlimited, bandpass 20-4000 Hz) and sampled at 1000 Hz.
A chin rest centered between the manipulanda was used to maintain a consistent head position throughout the trials. An oscilloscope was positioned in the center of a white opaque screen 66 cm in front of the chin rest and displayed the angular position of the aiming arm as a dot 1 mm in diameter, as well as the start position, central fixation point and the target region. The imperative stimuli were two green LEDs positioned at an eccentricity of 10° on either side—and on the same horizontal plane—of the fixation point displayed on the oscilloscope screen. A 1 mm dot positioned near the top of the oscilloscope screen represented the starting position of the arm. The fixation point was a second dot 10 cm below the starting position dot and simultaneously represented the center of the target region. Movement of the manipulandum from the start position through an angular distance of 45° moved the response cursor from the start position to the fixation/target dot. Thus, a 4.5° angular displacement of the manipulandum resulted in a 1 cm movement of the response cursor. Two additional dots, equidistant above and below the fixation/target dot (0.33 cm, angular distance 1.5°) delineated the target region, subtending an angular distance of 3.0° around the target dot. A schematic representation of the visual display is presented in figure 2.4.

With this configuration, flexion of the aiming arm moved the response cursor from the top of the screen toward the bottom. This was the case regardless of whether the right-arm or left-arm controlled the cursor and thus maintained consistency in the display across movement conditions. A computer monitor positioned to the left of the opaque screen provided post-trial feedback regarding movement accuracy and movement time of the aiming arm. No feedback was provided regarding the mirroring arm.
Figure 2.4. Schematic representation of the visual display for experiment 1. Upper black dot on oscilloscope is the response cursor. Flexing the aiming arm moves the dot from the top of the screen toward the target region at the bottom. The lower black dot is the center of the target region and the visual fixation point. The gray dots are the LEDs used for the visual stimuli positioned 10° to the left and right of the fixation point. The arrow above the right hand shows the direction of arm movement.
2.2.3. Procedures

Subjects were seated in a dimly lit room with their arms positioned on the manipulanda and the height of the chair and chin rest adjusted for comfort. Subjects were instructed to perform the movements as quickly as possible while emphasizing accuracy. On bilateral trials they were given the additional instruction to initiate the movements of both arms simultaneously. Each subject performed three sets (one practice, two experimental) of four blocks of trials, each block in a set corresponding to one of the following movement conditions: unilateral right-arm aiming (UR), unilateral left-arm aiming (UL), bilateral right-arm aiming (BR), bilateral left-arm aiming (BL). In the unilateral conditions, only one arm was used, while both arms were used in the bilateral conditions. The only difference between the two bilateral conditions was the arm controlling the response cursor. In the practice set, a minimum of five trials were performed in each block, the block order being counterbalanced across subjects. These trials were not submitted to statistical analysis. The condition order of the first set of experimental trials was counterbalanced across subjects and the order of the second set of experimental trials was the reverse-order of the first. Thirty-four trials were accepted in each block. The first trial constituted a familiarization trial to control for cross-over effects from the previous condition and was not included in the analysis. The remaining 33 trials consisted of 15 left-stimulus trials, 15 right-stimulus and 3 'catch' trials with the order of the trials being randomly determined.

During the practice trials, eye position was monitored using an infrared eye track system (Applied Systems Laboratories System 4000) to ensure that subjects were able to properly fixate the target/fixation point. All subjects fixated the target position without any unwanted eye movements. Following the practice trials the eye track system was removed for the
remainder of the session and subjects were continuously reminded to fixate the target position prior to presentation of the stimulus.

A trial began with the experimenter giving a verbal "ready" signal informing the subject to fixate the target position. After a brief delay (approx. 1-2 seconds), a variable foreperiod (500-2500 ms) was initiated by an auditory tone (100 Hz, duration 200 ms) followed by a flash of either the right or left LED (duration 100 ms). No flash occurred on the catch trials. To control for any potential influence of foreperiod duration on reaction time, the foreperiods for right and left stimuli were matched within each block of trials.

Following each trial a search was performed on the velocity trace of each limb to locate the time of movement onset, defined as the time at which the angular velocity of the manipulandum first exceeded 8°/s. Trials in which the movement onset of one or both arms was less than 100 ms or greater than 500 ms were discarded as anticipation and lapses of attention respectively and subsequently repeated. Additionally, bilateral trials were checked to ensure that the difference in onset time between right and left arms did not exceed 50 ms. None of the trials for any subject exhibited left-right asynchrony in excess of this criterion. A second search was then performed to locate the point at which the angular velocity of the manipulandum first fell below 8°/s. This point defined the end of the movement and was used to determine movement time (MT) and movement distance (MD). Feedback regarding MT (in milliseconds) and accuracy ("On target"; "Target Undershoot: X degrees"; "Target Overshoot: X degrees") of the aiming arm was provided to the subject after each trial on a computer monitor situated to the left of the white screen. No feedback was provided regarding the mirroring arm on bilateral trials.
2.3. Dependent measures and data analysis

The primary dependent measure was premotor reaction time (PRT) defined as the point at which the biceps EMG first began a sustained rise above baseline levels. The location of this point was obtained through visual inspection of the individual EMG traces for each trial using the following procedure. The first 500 ms of the rectified EMG was displayed on a computer monitor using a custom interactive software program along with angular displacement and angular velocity from which movement onset was determined. A filtered version of the EMG trace (10 ms moving average) was superimposed on top of the rectified trace, as was a line indicating two standard deviations above baseline activity measured during the 100 ms preceding presentation of the imperative stimulus. This was defined as the location where the filtered EMG first began a sustained rise above baseline. Onset was determined by locating the point where the filtered EMG first rose above the two standard deviation line and then locating the point on the rectified trace where activity first increased. An example is presented in figure 2.5. Because of the very high correlation between PRT and RT (r = 0.97) only PRT was submitted to statistical analysis. This was the case for the present experiment, as well as the remaining experiments in this thesis. The remaining dependent measures were movement time (MT), movement distance (MD) and variable error (VE) were determined from the kinematic analysis conducted during the experiment. Variable error is simply the standard deviation about the individual subjects' movement endpoints.

Because many experiments using a crossed-uncrossed paradigm rely on medians as the measure of central tendency for reaction time (Aglioti et al., 1991; Di Stefano et al., 1980, 1992; Iacoboni & Zaidel, 1999), statistical analyses of PRT were conducted with both
Figure 2.5. Example EMG showing location of premotor time (arrow). The solid vertical line denotes the time of presentation of the stimulus. The broken horizontal line indicates two standard deviations above baseline activity.
medians and means to allow a direct comparison to these previous experiments. For the
kinematic measures, only mean values were statistically analyzed. This procedure was used
for each of the remaining experiments in this thesis.

Each dependent measure was analyzed with separate three-way repeated measures
ANOVAs. The factors were hand (left, right), movement condition (unilateral (UN),
bilateral (BI)) and stimulus position (crossed, uncrossed). Where applicable, post-hoc tests
were conducted using separate paired t-tests with the critical t-value determined according to
the procedure of Keppel (1973). The critical t-value was calculated according to the equation
t_{crit} = q/\sqrt{2}, \text{ where } q \text{ is the studentized range statistic for the total of number of means in the
ANOVA and the degrees of freedom of the individual t-tests. Significance was assumed if
the obtained } t_{value} \text{ exceeded the calculated critical } t_{value}.

2.4. Results

2.4.1. PRT

For median PRT the third-order interaction was not significant, F(1,11) < 1. Thus, the
interaction between stimulus position and movement condition did not differ between the left
and right hands. Neither the second-order interaction of hand and movement condition,
F(1,11) < 1, nor the interaction of hand and stimulus position, F(1,11) < 1, was significant.
Most important to this thesis, the interaction of movement condition and stimulus position
failed to reach significance, F(1,11) = 3.6, p > 0.05. Thus, the effect of stimulus position on
reaction time did not differ between unilateral and bilateral movements. The only main
effect to reach significance was the effect of stimulus position, F(1,11) = 27.1, p < 0.001.
Analysis of this effect revealed that movements of the aiming arm were initiated more
quickly when uncrossed stimuli were presented (204.1 ms, +/- 28.1) than when crossed stimuli were presented (212.6 ms, +/- 30.1) (see figure 2.6a). Neither the main effect of hand, $F(1,11) = 3.3$, $p > 0.05$, nor the main effect of movement condition, $F(1,11) = 3.1$, $p > 0.05$, was significant.

The results from mean PRT were very similar to those for median PRT. Again, only the main effect of stimulus position was significant, $F(1,11) = 14.7$, $p < 0.01$, with movements being initiated more quickly to uncrossed stimuli (211.7 ms, +/- 27.7, crossed 218.8 ms, +/- 28.8) (see figure 2.6b). The interaction between movement condition and stimulus position was not significant, $F(1,11) = 2.7$, $p > 0.05$. Thus, regardless of whether bilateral or unilateral movements were performed, movements were initiated more quickly in response to uncrossed stimuli. This observation is consistent with the evidence from Jakobson et al. (1994) and the prediction of Todor et al. (1982) that task requirements influence whether ipsilateral or contralateral pathways are used.

### 2.4.2. MD

Both the left and right arms terminated the movements very close to the target. In fact, all the mean values were within the required target region (left UN 46.2°, +/- 0.83; right UN 45.8°, +/- 0.97; left BI 45.8°, +/- 0.90; right BI 45.7°, +/- 0.73) (see figure 2.7a). Thus, the subjects were able to accurately control the position of the arm. With respect to statistical analysis, none of the interactions or main effects were significant. Thus, accuracy appears to be similar (i.e., not statistically different) across both movement conditions and both stimulus positions. However, there was a trend toward longer movement distances when responses were made to crossed stimuli, $F(1,11) = 4.8$, $p = 0.051$, although the mean difference
Figure 2.6. (a) Median and (b) mean PRT plus standard error for the main effect of stimulus position. Responses were initiated more quickly to uncrossed stimuli indicating that arm movements were always controlled by the contralateral hemisphere.
Figure 2.7. (a) Mean movement distance, (b) movement time and (c) variable error plus standard errors for the aiming arm.
between the two stimulus conditions was very small (crossed 46.0°, +/- 0.76; uncrossed
45.8°, +/- 0.83).

2.4.3. MT

The interaction between hand and stimulus position was significant, F(1,11) = 11.5, p < 0.05. This is presented in figure 2.7b. From a visual inspection it appears the interaction is due to the left hand taking more time to complete the movements in response to crossed stimuli (318 ms, +/- 64.4 vs. 311 ms, +/- 57.5), while for the right hand there was little difference between the two stimulus positions (crossed 299 ms, +/- 54.7; uncrossed 304 ms, +/- 57.2). Post-hoc testing revealed that only the difference between the right and left hands in response to crossed stimuli was significantly different. Thus, when the stimulus was crossed to the left hand, movements took slightly longer to complete. It is also apparent from figure 2.7b, that regardless of movement condition the right hand (302 ms, +/- 55.6) completed movements more quickly than the left (315 ms, +/- 51.2). Overall, this right hand advantage was reliable according to the ANOVA, F(1,11) = 7.5, p < 0.05. This overall advantage of the right hand for movement completion is consistent with a number of other studies (Bradshaw et al., 1990; Hodges et al., 1997; Roy et al., 1994;).

2.4.4. VE

For both arms, spatial variability was quite low, further attesting to the subjects' ability to perform accurate movements (see figure 2.7c). There were no significant main effects or interactions for variable error, although there was a trend towards variability being reduced when bilateral movements were performed (UN 3.5°, +/- 0.57, BI 3.2°, +/- 0.56), F(1,11) = 4.8, p = 0.051. This, in combination with the lack of significant effects for movement condition suggests that the left and right hands were able to complete the movements with
similar overall levels of accuracy and endpoint consistency. Based on the work of Jakobson et al. (1994), had the arm movements come under control of the ipsilateral hemisphere it might have been expected that there would have been more variability in the movement due to the reportedly lesser efficiency of such control. That this was not the case suggests that, consistent with PRT, arm movements were controlled by the contralateral hemisphere regardless of movement condition.

2.5. Discussion

It is commonly assumed that movements of the upper limbs, especially the hands, are affected through crossed motor pathways from the contralateral cerebral hemisphere. Evidence to support this view is the severe motor impairments that occur on the contralateral side of the body accompanying unilateral brain injury (Colebatch & Gandevia, 1989) and the inability to accurately shape the hands and fingers for a precision grip when the hand is guided by the ipsilateral hemisphere. However, there is a substantial body of literature suggesting that the ipsilateral hemisphere can control arm movements, especially movements involving proximal and axial musculature. Brinkman and Kuypers (1973) demonstrated that split-brain monkeys were able to effectively control a reaching movement via the ipsilateral hemisphere and concluded that these movements were controlled through ipsilateral descending pathways. Jakobson et al. (1994) provided similar evidence of ipsilateral control of reaching movements in acallosal subjects. Additional evidence of ipsilateral control has been obtained using crossed-uncrossed paradigms (Aglioti et al., 1993; Di Stefano et al. 1980). Reaction times to crossed visual stimuli are typically slower than reaction times to uncrossed stimuli for unilateral and bilateral hand movements and unilateral arm movements. However, this difference disappears when bilateral arm movements are executed. Because
the longer reaction times in response to crossed stimuli is thought to reflect interhemispheric
transfer of stimulus information (Berlucchi et al., 1994), the failure for crossed reaction time
to exceed uncrossed reaction time when bilateral proximal movements are performed has
been interpreted as evidence that proximal muscles can access bilaterally distributed
pathways. By accessing these pathways, the movements of both arms are initiated
simultaneously by the hemisphere receiving the visual stimulus eliminating the need for
interhemispheric transfer.

Despite evidence that proximal muscles can be controlled through ipsilateral pathways,
it has been assumed that such control is less efficient than contralateral control. While
Jakobson et al. (1994) reported that acallosal subjects could successfully complete reaches
under guidance of the ipsilateral hemisphere, these movements took substantially longer to
complete than movements under guidance of the contralateral hemisphere. They concluded
that while ipsilateral control is possible for the proximal muscles, it is much less efficient
than contralateral control. Thus, it might be expected that when a muscle can be accessed
through both ipsilateral and contralateral pathways, the pathway used will be dependent on
the nature of the task (Todor et al., 1982). However, it is possible that the prehension task
used by Jakobson et al. (1994) might underestimate the efficiency of ipsilateral control and
that a different task, in particular one requiring bilateral movements, might reveal a greater
ability for ipsilateral control. If this is correct, the first assumption of the model presented in
this thesis, that the requirement to execute spatially precise movements restricts control to the
contralateral hemisphere, would be invalid. Thus, experiment 1 was conducted to determine
if this assumption is, in fact, tenable.
In experiment 1 subjects performed elbow flexion movements in both unilateral and bilateral conditions in response to a lateralized visual stimulus. Previous experiments using this paradigm have demonstrated that movements involving proximal muscles can be initiated equally well by either hemisphere through bilaterally distributed pathways when bilateral movements are performed (Aglioti et al, 1993; Di Stefano et al., 1980). However, these experiments did not emphasize the quality of movement. It is assumed here that having to execute a spatially precise movement will restrict control to the contralateral hemisphere. Thus, even if ipsilateral pathways are available, the movement will still be controlled through contralateral pathways. The results of this study support this assumption.

Overall, movements of the aiming arm were initiated more quickly in response to uncrossed stimuli than to crossed stimuli. If the movement could be sufficiently controlled through ipsilateral pathways the reaction time advantage to uncrossed stimuli would be abolished when bilateral movements were performed yielding a significant interaction between stimulus position and movement condition. However, this interaction did not reach significance for either median PRT nor mean PRT, while the main effect of stimulus position was significant for both measures. Hence it can be concluded that the requirement to execute accurate movements restricts control to the contralateral hemisphere, even when bilateral movements are required.

Additional support for this conclusion is provided by the analysis of spatial precision. Neither movement distance, nor variable error, was affected by the position of the imperative stimulus in the unilateral and bilateral movements. Had the aiming arm been controlled via the ipsilateral hemisphere when crossed stimuli were presented, one might have expected an increase in endpoint variability and/or reduced movement accuracy (cf. Jakobson et al.,
That no such effect was apparent is consistent with contralateral control of the aiming arm across all movement conditions. While movement times were affected by stimulus position, as indicated by a significant hand by stimulus position interaction, the differences were extremely small and post-hoc tests failed to reveal any significant differences between means. Considering the rather large increase in movement time associated with ipsilateral control reported by Jakobson et al. (1994), the differences in movement times observed here seem unlikely to reflect differential hemispheric control.

In summary the present experiment provides support for the assumption that the aiming arm is controlled predominantly by the contralateral hemisphere, irrespective of whether unilateral or bilateral movements are performed. Thus, the increase in reaction time when BL movements were performed in our earlier study (Garry & Franks, 2000) were unlikely to have resulted from differences in the control of the aiming hand. Experiments 2 and 3 will further test the predictions of the model for the control of both proximal and distal arm movements.
3. Experiment 2: The control of spatially constrained unilateral and bilateral movements involving distal muscles

3.1. Introduction

There is a general consensus in the literature that the proximal muscles of the arm can be controlled through ipsilateral descending pathways (Aglioti et al., 1993; Brinkman & Kuypers, 1973; Di Stefano et al., 1980). In fact, it is precisely this evidence that led to the hypothesis of the present thesis (Garry & Franks, 2000). In contrast, it is typically believed that the distal muscles of the arm, especially those of the hands and fingers, have no access to these ipsilateral pathways and are controlled exclusively through crossed pathways from the contralateral hemisphere. Differences in innervation of the proximal and distal musculature have been used to account for the greater deficits in the performance of the hands relative to the arms when control is restricted to the hemisphere ipsilateral to the responding limb. The split brain monkeys discussed by Brinkman and Kuypers (1973) were able to perform the reaching phase of movements under the control of the ipsilateral hemisphere with a reasonable degree of accuracy. In stark contrast, the performance of the hands and fingers were severely impaired. There was little anticipatory grip formation of the fingers and the hands were seen to move as if ‘blind’. Only once contact was made with the object were the hands able to form a proper grip. This led to the conclusion that the ‘seeing’ ipsilateral hemisphere was unable to exert a direct influence on the control of the hand muscles.

Jakobson et al. (1994) reached a similar conclusion in their study of acallosal subjects. When subjects were required to execute a prehension movement under the guidance of the ipsilateral hemisphere, deficits in grip formation were observed. It was argued that the ipsilateral ‘seeing’ hemisphere was unable to exert effective control over the hand to allow efficient grip formation. Because the reaching phase of the movement successfully brought
the hand toward the object, however, they, like Brinkman and Kuypers (1973), concluded
that the proximal muscles can be controlled by the ipsilateral hemisphere, although they did
note that even the reach component was impaired relative to conditions involving
contralateral control.

Despite the evidence from these studies that ipsilateral control of the distal muscles is
relatively weak, there are a number of studies that appear to support the existence of
ipsilateral control of the distal musculature, even for the muscles of the hands. Volpe et al.
(1982) had split-brain patients mimic hand postures presented visually to a single hemisphere
with the hand ipsilateral or contralateral to the stimulated hemisphere. As one might expect
based on the previous discussion, performance was substantially better when the hand
contralateral to the stimulated hemisphere was used. However, there was evidence of at least
some ipsilateral control as performance in the ipsilateral condition was above chance. A
similar paradigm was later used by Trope et al. (1987) with the same results. In addition,
they found that ipsilateral control was best for the index finger and thumb and was poor for
the other fingers.

More recently, TMS has been used to investigate the existence of ipsilaterally
descending pathways to the muscles of the arm and hand. Wasserman et al. (1991, 1994)
as able elicit both ipsilateral motor evoked potentials (MEPs) and ipsilateral silent periods
in the first dorsal interosseous muscle, as well as in the deltoid muscle. Ziemann et al. (1999)
have also been able to elicit ipsilateral responses in distal as well as proximal musculature.
Consistent with Wasserman et al. (1991, 1994) excitatory responses were readily obtained in
the FDI muscles in both normal subjects and in one subject with total callosal agenesis. That
ipsilateral responses were able to be evoked in the acallosal subject is strong evidence that
these responses are mediated through ipsilateral pathways and are not due to a spread of excitation to the contralateral hemisphere via the corpus callosum. An additional observation in this study was that different muscles appear to be differentially represented in the ipsilateral hemisphere. While excitatory responses could be evoked from FDI, wrist extensor and biceps brachii muscles, no excitatory responses could be evoked in the opponens pollicis muscle, wrist flexors and triceps muscle. This might indicate that ipsilateral control is stronger for certain muscle groups than for others. Consistent with this, Colebatch and Gandevia (1989) observed that decrements in muscle strength of hemiparetic patients for the arm contralateral to the lesion was most severe for the hand and wrist flexors and less so for wrist extensors and shoulder adductors. The less extreme deficits for the latter muscles can be accounted for if the unaffected hemisphere ipsilateral to the paretic arm has more substantial ipsilateral control over these muscles allowing a relative sparing of muscle strength.

Another recent investigation by Chen et al. (1997) used repetitive TMS to investigate the influence of the ipsilateral hemisphere on the control of the hands during complex tasks. Subjects performed sequential key presses on a piano keyboard using either a simple or a complex sequence. The simple sequence involved alternate pressing of adjacent keys in an ascending and then descending order, while the complex sequence involved a relatively random pattern of key presses. Both tasks required 16 key presses to be performed in a 2 second period. Performance was assessed by analyzing the frequency of both key press errors and timing errors. Compared to the control condition, TMS induced errors in key pressing only when delivered over the contralateral hemisphere in the complex task. However, timing errors were observed in both the simple and complex tasks with stimulation
over both the contralateral and ipsilateral hemispheres. In addition, the effect was greatest with stimulation over the left hemisphere suggesting a greater involvement of the left hemisphere in the control of both limbs regardless of movement condition. The authors concluded that the hemisphere ipsilateral to the responding hand does play a role in movement control.

In light of this evidence, the present experiment was designed to assess whether a task involving distal muscles of the arm would be influenced by the different movement conditions used in our first experiment (Garry & Franks, 2000) in the same way that movements of proximal muscles are. To this end, a wrist extension task was used based on the evidence that the wrist extensors are innervated by ipsilateral pathways (Colebatch & Gandevia, 1989; Ziemann et al., 1999). If the left hand, when mirroring, can be controlled by the ipsilateral hemisphere, the same pattern of results should be observed as in our earlier experiment. Specifically, reaction times should increase when bilateral movements requiring left-arm precision are performed, but not when movements requiring right-arm precision are performed. By contrast, if the wrist extensors can be controlled only through contralateral pathways, then, according to the transcallosal inhibition hypothesis, reaction times for both bilateral movement conditions should exceed that for unilateral movements.

It is important to note, however, that a successful replication of the results of our earlier study would confirm only that the mechanism involved in movement initiation is similar for both distal and proximal arm muscles. In and of itself, this can neither confirm nor refute the hypothesis that changes in the hemispheric control of the arms across the tasks is responsible for the observed pattern of reaction times. However, a supportive result would be beneficial for experiment 3 in that it would provide justification for testing both the elbow flexor and
wrist extensor muscles in a TMS paradigm that can directly assess hemispheric control, thereby improving the generalizability of the results.

An additional factor tested in this experiment was the effect of providing feedback regarding movement accuracy and movement time from the end of the movement, following error corrections rather than from the initial impulse phase of the movement. In our first experiment (Garry & Franks, 2000), and in experiment 1, movement time and accuracy were determined from the initial impulse phase. The initial impulse$^2$ is the phase of the movement from initiation to the first positive-to-negative zero line crossing in velocity.$^3$ Because this phase of the movement is thought to be pre-programmed and carried out without the aid of feedback (Meyer et al., 1988; Woodworth, 1899) spatial accuracy will depend entirely on the precision of the programmed response. Thus, the hemisphere best able to precisely execute the limb movement would necessarily have to initiate the movement of that limb. If movement accuracy was determined from the error correction phase of the movement, the precision required in the initial impulse phase might not need to be as high as sufficient time would be available to use feedback to achieve terminal accuracy.

Potentially, such a control scheme could allow one hemisphere to participate in response initiation and the other hemisphere to take over control later in the movement when visual (and kinesthetic) feedback is available and precise error corrections are needed. A similar suggestion was made by Beaubaton, Grangetto and Paillard (1979) to explain ipsilateral reaching performance in split-brain monkeys. They suggested that the ipsilateral ‘seeing’

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$^2$ For clarity it is important to note that this use of the term impulse is not synonymous with impulse in the mechanical sense, which is the integral of force over time.

$^3$ Experimentally, this phase was defined as the position where velocity dropped below 8° per second and therefore maintained symmetry between the determination of movement onset and movement ‘termination’.
hemisphere could "use positional cues to trigger the program for the ballistic part of an
ipsilateral pointing movement, and the contralateral ‘arm-seeing’ hemisphere [could] use
movement cues to compensate... for the deficit of the terminal adjustment" (pp. 381-382).
Such control might allow the left hemisphere to initiate the movement of the left arm in the
BL movement condition and the right hemisphere to take over when feedback processing is
required. If this were to happen, reaction time increases in the BL movement condition
would be abolished.

3.2. Methods

3.2.1. Subjects

A total of ten participants volunteered for this experiment (7 male, 3 female, range 18-32
years). All participants were right handed according to the Edinburgh Handedness Inventory
(Oldfield, 1971) and had normal or corrected to normal vision. All participants were free of
neurological and neuromuscular disorders.

3.2.2. Apparatus

Participants were seated in a comfortable chair that was height adjustable and positioned
between two identical wrist manipulanda. Each manipulandum consisted of an arm support
and hand support which could be clamped around the hand to prevent unwanted movement.
The hand support was attached to a vertical axle that limited wrist rotation to the horizontal
plane. The two manipulanda were oriented at angle of 15° to the left and right of body
midline for the left and right manipulandums, respectively. This position was used as it was
found to be more comfortable than orienting the manipulanda parallel to body midline. The
arms were positioned such that wrist joints were collinear with the axis of rotation and the
hands were firmly clamped in the supports. Displacement was measured via identical optical
encoders (Dynapar model E2025001303) attached to the axle of each manipulandum and sampled at 2000 Hz using a 12-bit A/D converter. Velocity was obtained by low-pass filtering displacement (20 Hz, Butterworth) followed by differentiation. Mechanical stops were used for the starting positions and were placed such that the wrists were flexed approximately 20°. This position ensured that the wrist could extend comfortably through a relatively large range of motion without being impeded by biomechanical factors. Target movement distance was 45°.

An oscilloscope positioned directly in front of the subject (distance approximately 50 cm) displayed the target region and a response cursor (1 mm diameter) whose position was controlled by moving either the left or right manipulandum, depending on the movement condition. For left-hand aiming movements the left hand controlled the cursor with the target region positioned on the left side of the oscilloscope screen and the start position on the right. Extension of the wrist moved the cursor from right to left congruent with wrist movement. This mapping was reversed when the right hand controlled the cursor. The experimental setup is illustrated schematically in figure 3.1. EMG from the wrist extensors and wrist flexors were recorded using pre-amplified, differential electrodes (8-mm-diameter, spaced 2 cm apart). The signals were amplified (X 2000, Therapeutics Unlimited) and sampled at 2000 Hz using a 12-bit A/D converter. A ground electrode was fixed to the left lateral malleolus.

3.2.3. Procedures

Each participant completed two blocks of 23 trials in each of the following four movement conditions; unilateral left (UL), unilateral right (UR), bilateral left aiming (BL) and bilateral right aiming (BR). Three trials in each block were ‘catch’ trials on which the
Figure 3.1. Schematic of the experimental setup for experiment 2. The arrow above the right hand shows the direction of hand movement. Extension of the right wrist moves the black response cursor into the target region (vertical lines).
imperative stimulus did not occur. These were used to discourage anticipation of the imperative signal. If a movement was detected on these trials the participant was reminded to wait for the go signal before initiating the movement.

A minimum of five practice trials were given in both the UL and UR movement conditions prior to beginning the session in order for the participants to become familiar with the task. At the beginning of a new movement condition, one or two 'practice' trials were provided to eliminate any cross-over effects from the previous condition. These trials were not submitted to statistical analysis. Following the practice trials, subjects completed one block of each movement condition. For all subjects, the first set of blocks were performed with feedback of movement time and accuracy determined from the end of the initial impulse (II condition). This ensured a replication of the conditions of our earlier experiment. For these movements, corrections in the movement trajectory were not able to contribute to the accuracy of the movement endpoint. Following this, a second set of blocks was given in reverse order of the first with feedback determined from the end of the error correction phase (EC condition). The movement endpoint was defined as the first point in the movement where the velocity of the manipulandum fell below 8%/s and remained below this velocity for 150 ms. For both feedback conditions, only the kinematic measures obtained from the initial impulse phase were submitted to statistical analysis.

Participants were instructed to move the cursor from the start position to the target region as quickly and accurately as possible and were informed that they were to minimize their reaction time. For bilateral trials they were further instructed to initiate the movements of both wrists simultaneously, but that once the movement was underway they should emphasize precision of the aiming hand. A trial began with a warning tone (200 Hz, 200 ms)
followed by the go signal (1000 Hz, 100 ms) after a fixed foreperiod of 1000 ms. Trials on
which movement was initiated within 100 ms or more than 500 ms following the imperative
stimulus were discarded as anticipation and lapses of attention. Trials on which this occurred
were discarded and subsequently repeated. This accounted for fewer than 1% of total trials.

3.2.4. Dependent measures and data analysis

The dependent measures were premotor time (PRT), movement distance (MD),
movement time (MT) and variable error (VE). The latter three measures were determined
from the end of the initial impulse phase of the movement in both feedback conditions.
These were determined in the same way as for experiment 1. Statistical analysis was
performed using separate three-way repeated measures ANOVAs with hand (left, right),
movement condition (UN, BL, BR) and feedback condition (II, EC) as factors. Post-hoc tests
were conducted using the same procedure as in experiment 1. As with experiment 1, both
median and mean PRT were submitted to statistical analysis. Analysis of movement distance
was performed only on the initial impulse phase of the movement.

3.3. Results

3.3.1. PRT

For median PRT only the main effect of movement condition, F(2,18) = 3.6 p < 0.05,
was statistically significant. Overall, reaction times were longer when BL movements (140.7
ms, +/- 39.8) were performed compared with UN (133.2 ms, +/- 34.2) and BR (134.5 ms, +/-
36.3) movements (see figure 3.2a). This pattern is consistent with the results of our earlier
study (Garry & Franks, 2000) and suggests that the mechanism responsible for the increased
reaction times when BL movements are performed is similar for both proximal and distal
muscles. In terms of the present thesis the interpretation is that the greater reaction time for
Figure 3.2. (a) Median and (b) mean premotor time (PRT) plus standard error for the main effect of movement condition. Main effect is significant for both measures (p < 0.05). Post-hoc testing yielded significant differences between BL and BR in (b).
BL movements reflects the influence of transcallosal inhibition. That PRT did not increase for BR movements relative to unilateral movements is consistent with ipsilateral control of the left arm, thereby avoiding transcallosal inhibition and the accompanying increase in reaction time. While the ANOVA yielded a significant $F$ for the effect of movement condition, post-hoc analysis failed to reveal any significant differences among the three movement condition means.

None of the effects involving feedback condition were significant. This indicates that the movements were initiated in a similar manner regardless of the phase of the movement from which accuracy was required. Thus, the increase in reaction time appears to be relatively independent of whether terminal accuracy is achieved via feedback processing or whether it must be programmed into the initial impulse phase of the movement. It can therefore be argued that, at least for the fast and relatively short-duration movements used in this experiment, hemispheric control is unaffected by the degree of accuracy required in the initial impulse phase of the movement. However, this conclusion must be tempered somewhat as all subjects performed the II feedback condition first, followed by the EC feedback condition. It might be that the subjects simply developed a strategy to achieve accuracy with the initial impulse and maintained this strategy in the EC movement condition.

The analysis of mean PRT revealed a very similar pattern to that obtained for median PRT. Movement condition was the only factor to have a significant effect on reaction time, $F(2,18) = 4.2, p < 0.05$, with BL movements having the longest reaction times (BL 150.5 ms, +/- 38.6; UN 143.8 ms, +/- 36.4; BR 142.7 ms, +/- 39.8) (see figure 3.2b). Unlike the analysis of median PRT, however, post-hoc tests revealed a significant difference between the BL and BR movement conditions.
3.3.2. MD

While both arms terminated the movements near the target when aiming movements were performed, both hands tended to overshoot the target when mirroring movements were performed. In addition, the amount by which the mirroring arm overshot the target differed between the two feedback conditions yielding a significant third-order interaction, $F(2,18) = 3.8, p < 0.05$. This is presented in figure 3.3. To simplify analysis of the interaction additional two-way ANOVAs were performed separately for each hand with movement condition and feedback condition as factors. For the left hand, the ANOVA yielded significant main effects both for feedback condition, $F(1,9) = 15.1, p < 0.01$, and movement condition, $F(2,18) = 25.0, p < 0.001$. The interaction between feedback and movement condition was not significant, $F(2,18) = 2.0, p > 0.05$. Analysis of the effect of feedback condition reveals that, overall, the left hand traveled further in the EC feedback condition ($50.0°, +/- 2.1$) than in the II movement condition ($48.8°, +/- 2.2$). While this might reflect a greater need for accuracy in the II condition, it must be pointed out this effect includes both the aiming and mirroring hands. Inspection of figure 3.3a suggests that the majority of this difference was due to the mirroring arm traveling further in the EC condition ($58.4°, +/- 7.6$) compared with the II condition ($55.9°, +/- 6.7$). With respect to the movement condition effect, the left hand traveled further in the BR ($57.2°, +/- 6.9$) movement condition (mirroring), than in both the UN ($45.5°, +/- 1.0$) and BL ($45.6°, +/- 0.6$) movement conditions which did not differ from one another. Thus, when the left hand was aiming (UN and BL movement conditions) the initial impulse phase of the movement terminated very close to the target, whereas the target region was overshot, and considerably more variable, when the hand was mirroring.
Figure 3.3. Mean movement distance plus standard error for the significant third-order interaction ($p < 0.05$) of hand, movement condition and feedback condition. (a) Left hand, and (b) right hand. Both hands were accurate when aiming, but overshot when mirroring.
For the right hand (figure 3.3b), the interaction between feedback condition and
movement condition was significant, F(2,18) = 11.0, p < 0.01. Post-hoc tests yielded a
pattern very similar to that for the left hand. For both feedback conditions, movement
distance was greater when the right hand was mirroring than when it was aiming. Thus, for
the II movement condition, BL movements (58.3°, +/- 8.4) overshot the target while both UN
(46.1°, +/- 0.9) and BR movements (46.3°, +/- 1.2) terminated very close to the target. The
same pattern can be observed for the EC movement condition with BL movements (54.3°,
+/- 6.6) again overshooting the target while both UN (46.4°, +/- 0.9) and BR movements
(46.0°, +/- 1.2) terminated close to the target. The interaction appears to result from BL
movements overshooting the target more in the II movement condition than in the EC
movement condition, although this difference was not significant according to post-hoc tests.

3.3.3. MT

The main effect of movement condition was significant, F(2,18) = 7.6, p < 0.01, for
movement time. Overall, the two bilateral movement conditions took longer to complete
than the unilateral movement conditions (BL 248.7 ms, +/- 50.9; BR 251.5 ms, +/- 52.9; UN
235.0 ms, +/- 42.7). However, this must be interpreted in light of a significant hand by
movement condition interaction, F(2,18) = 12.2, p < 0.001 (see figure 3.4a). Post-hoc
analysis of the interaction revealed a pattern that mirrors that observed for movement
distance. For the right hand, movement times were greater when BL movements (262.2 ms,
+/- 51.2) were performed compared with both the UN (233.4 ms, +/- 37.9) and BR
movement (234.4 ms, +/- 45.9) conditions, which did not differ significantly. For the left
hand the pattern was essentially the same in the sense that mirroring movements had longer
movement times. When the left hand was mirroring (BR condition) movement times tended
Figure 3.4. (a) Mean movement time and (b) variable error plus standard error. Both hands took longer to complete mirroring movements (left BR, right BL) and were more variable in the II feedback condition.
to be longer (268.6 ms, +/- 63.9) than when the left hand was aiming (UN 236.6 ms, +/- 48.4; BL 235.5 ms, +/- 53.4). However, only the difference between the BR and UN movement conditions reached significance. Neither the interaction between hand and feedback condition, F(1,9) < 1, nor the interaction between feedback condition and movement condition, F(2,18) = 1.5, p > 0.05, was significant.

3.3.4. VE

Regardless of movement condition, both the left and right hands terminated the movements with a relatively low amount of spatial variability. This was the case both for aiming movements (left UN 3.7°, +/- 1.0; BL 4.0°, +/- 1.2; right UN 3.8°, +/- 0.9; BR 4.1°, +/- 1.0) and mirroring movements (left BR 4.5°, +/- 1.3; right BL 4.7°, +/- 1.5). Thus, although both arms tended to overshoot the target region when executing mirroring movements, the movements were, nonetheless, terminated with a high degree of consistency. This is reflected by the lack of significance for all main effects and interactions involving both hand and movement condition. However, the main effect of feedback condition was significant, F(1,9) = 5.9, p < 0.05, with II movements (4.4°, +/- 1.1) exhibiting greater variability than EC movements (3.8°, +/- 0.7). This is presented in figure 3.4b. It was expected that movements requiring accuracy of the initial impulse would be characterized by a lower variability for this phase of the movement compared with movements that rely on visual feedback for terminal accuracy. That this was not the case is somewhat surprising. However, given that EC condition was performed after the II condition by all subjects, the most parsimonious explanation is that it reflects a practice effect.
3.4. Discussion

The important finding from this experiment is that bilateral wrist movements requiring left-hand spatial precision display a deficit in reaction time compared with unilateral movements similar to that observed for proximal muscles (Garry & Franks, 2000). This represents a replication of the findings of our earlier study and suggests that movements of both proximal and distal limb segments are influenced by the movement condition in a similar manner. The deficit of reaction time in the BL movement condition is consistent with the transcallosal inhibition hypothesis (Ohtsuki, 1994). Because this increase is not observed for BR movements it is assumed that for this condition the movements of both arms are being initiated simultaneously by a single hemisphere, thereby eliminating the transcallosal inhibitory effect on reaction time.

Considering the task used in the present experiment involved the distal muscles of the arm, the preceding conclusion is open to debate. While there is a relatively large body of literature supporting the potential for ipsilateral control of proximal arm muscles (Aglioti et al., 1993; Brinkman & Kuypers, 1973; Colebatch & Gandevia, 1989; Di Stefano et al., 1980; Lavergne & Kimura, 1987), evidence consistent with ipsilateral control of distal muscles is admittedly more sparse. Hence, it is generally believed that distal muscles are controlled exclusively through contralateral pathways (Aglioti et al., 1993; Berlucchi et al., 1994; Brinkman & Kuypers, 1973). However, empirical support for the ipsilateral control of distal muscles is available. Recent TMS studies have demonstrated ipsilateral involvement of both hand and wrist muscles, in particular the wrist extensors (Wasserman et al., 1991, 1994; Ziemann et al., 1999). In addition, studies of split-brain patients have provided evidence consistent with the ipsilateral control of hand muscles (Trope et al., 1982; Volpe et al, 1987).
Taken together it seems reasonable to conclude, at least tentatively, that the results of the present experiment can be explained in terms of ipsilateral control in the BR movement condition.

An additional purpose of this experiment was to assess whether the effect of movement condition on reaction time would depend on the requirement for accurate termination of the initial impulse. In our earlier experiment (Garry & Franks, 2000), movement accuracy was determined from the end of the initial impulse phase of the movement. Because this phase is executed primarily open-loop (Meyer et al., 1988; Woodworth, 1899), terminal accuracy is dependent solely on the accuracy of the programmed movement. Hence, the hemisphere best able to execute a spatially precise initial impulse will be required to initiate the movement of the arm. Based on the study by Jakobson et al. (1994) and the results of experiment 1, this is expected to be the contralateral hemisphere. By contrast, if terminal accuracy can be refined using error corrections modified by visual feedback, the accuracy of the initial impulse will be less important. Thus, one hemisphere might be able to initiate the movement, while the other hemisphere could contribute to the terminal accuracy of the error correction phase (Beaubaton et al. 1979). In the context of the current task this might allow not only BR movements to be initiated by a single hemisphere, but also BL movements, thereby eliminating transcallosal in this condition. If this were to occur, reaction times in the EC movement condition would not be expected to follow the same pattern as in the II movement condition.

The results of the present experiment do not provide any support for this hypothesis. The phase of the movement from which accuracy was determined had no reliable effect on reaction time as illustrated by the lack of significant effects involving the feedback factor.
However, it is important to consider that all participants performed the II movement condition first followed by the EC movement condition. Thus, it might be argued that participants simply developed a strategy of accurately executing the initial impulse phase of the movement in the II condition and that this strategy was maintained in the EC movement condition. Certainly the lower variability of the initial impulse in the EC condition is consistent with this possibility. Despite this, it can, at least tentatively, be suggested that the phase of the movement from which accuracy is defined does not influence reaction time across the different movement conditions and does not affect the hemispheric control of arm movements.

In summary, for movements involving the distal muscles of the arm, the execution of bilateral movements results in an increase in reaction time when the movement requires left-arm precision, but not when it requires right-arm precision. This result is consistent with our previous study involving proximal arm movements (Garry & Franks, 2000) and suggests that the initiation of both distal and proximal movements is controlled by the same mechanism. In terms of the present hypothesis it is concluded that the increase in reaction time reflects transcallosal inhibitory mechanisms and that this inhibition is overcome when movements requiring right-arm precision are executed by accessing ipsilateral pathways to control the left arm.
4. Experiment 3: Hemispheric contributions to the control of unilateral and bilateral spatially constrained distal and proximal movements: A combined TMS and reaction time study.

4.1. Introduction

TMS was developed in 1985 by Barker (1985) as a non-invasive and painless means of stimulating neural tissue in conscious humans. The procedure relies on a rapidly changing, powerful magnetic field, produced by passing a large electrical current through a coil of wire, to stimulate cortical neurons. When positioned over the scalp, discharging a current through the coil creates a brief (time-to-peak ~ 100-200\(\mu\)s), but very powerful (peak 2.0 Tesla) magnetic field that activates cortical output neurons transynaptically (Rothwell, 1997). At sufficient intensity, stimulation of the motor cortex produces a measureable EMG potential in the muscles on the contralateral side of the body called a motor evoked potential, or MEP. Because TMS acts on neurons within the cerebral cortex, it is sensitive to changes in cortical excitability and is therefore an ideal tool for assessing changes in cortical involvement across different motor tasks.

A property of TMS stimulation that is of particular interest to the present experiment is its ability to transiently disrupt cortical processing (Pascual-Leone, Walsh & Rothwell, 2000). This is most apparent with repetitive, or rapid rate TMS (rTMS). With rTMS a train of several stimuli are delivered through the coil each second. This technique results in a temporary ‘lesion’ being induced in the cortical region underlying the coil allowing that area’s contribution to task performance to be assessed. This technique was used by Chen et al. (1997) to investigate ipsilateral motor cortex involvement in the control of simple and complex finger movements. Subjects were required to perform sequences of key presses on an electronic keyboard either in a simple or a complex pattern with both the right and left
hands. Performance was assessed by recording the number of key press errors and timing errors produced. During task execution, rTMS was delivered either over the right motor cortex or over the left motor cortex. For both performance measures the greatest effects were observed with contralateral rTMS. Both key press errors and timing errors increased significantly when contralateral rTMS was delivered. However, increases in timing errors were also observed with ipsilateral rTMS for both the simple and complex tasks. Of interest was the fact that the errors were greatest with stimulation of the left-hemisphere leading to the suggestion that the left hemisphere plays a greater role in the control of ipsilateral finger and hand movements than does the right hemisphere.

Another form of TMS is single-pulse TMS. This technique uses a single TMS stimulation rather than a train of stimuli. While this form of stimulation is not as efficient in inducing a temporary 'lesion', it nonetheless is able to activate inhibitory processes within the stimulated region of the cortex. The effect of this inhibition can be investigated using reaction time paradigms. When delivered over the region of the motor cortex controlling the responding muscle, single-pulse TMS produces a delay in reaction time. Day et al. (1989) observed increases in reaction time in excess of 50 ms when TMS was given during a wrist movement task. The magnitude of the induced delay is dependent both on the intensity of stimulation and the time of stimulation relative to the go signal. The larger the intensity of the stimulus and the closer the time of stimulation to the expected time of voluntary muscle activation the larger the observed delay (Taylor et al., 1995; Ziemann et al., 1997).

Ziemann et al. (1997) have reported that in these paradigms, TMS appears to produce two competing effects: one inhibitory and one facilitatory. When TMS is delivered simultaneously or slightly prior to the go signal in a reaction time task, a shortening of
reaction time is observed—in some cases by as much as 40-50 ms. This ‘facilitation’ of reaction time has been attributed to a sensory facilitation of the go signal with the auditory ‘click’ and ‘smarting of the skin’ that accompanies coil discharge (Romaiguère et al., 1997) rather than to a direct activation of intracortical facilitatory processes. When the stimulus is delivered more than 50 ms following the go signal, however, this facilitation is completely overcome and the inhibitory effects of TMS become apparent. Further increases in the delay between the go signal and TMS results in parallel increases in reaction time. Because the delaying influence of TMS over the motor cortex is maximal immediately preceding the voluntary response, Ziemann et al. (1997) concluded that TMS affects late cortical processes responsible for the release of a programmed movement. They suggested that the movement is released when “pre-movement facilitation in the motor cortex has increased above a certain threshold level” and that TMS produces inhibition in this ‘release channel’ (p. 38).

The delay of reaction time associated with TMS stimulation is specific to the involvement of the stimulated region in task production and is not a general effect of TMS. Taylor et al. (1995) observed that movement of the coil away from the optimal site for evoking contralateral MEPs resulted in an associated reduction in the ability of TMS to influence contralateral reaction time. Thus, for TMS to delay reaction time, the stimulus must be delivered over the brain region directly involved in the control of the muscle. Day et al. (1989) concluded that TMS exerts its effect not through a generalized influence on the subject’s intention to respond, but by “inhibiting a group of strategically placed neurons in the brain (probably in the motor cortex)” that are responsible for initiating the programmed movement. Thus, stimulation of neurons other than those motor cortical neurons responsible for movement initiation will have little effect on reaction time.
The present experiment takes advantage of the specificity of TMS for producing reaction time delays to directly assess the involvement of the left and right motor cortex in the tasks used in our previous experiments (Garry & Franks, 2000). The assumption is that TMS delivered over the motor cortex controlling the responding limb will produce a measurable delay in reaction time. Based on the results of experiment 1, for both the unilateral and bilateral movement conditions TMS contralateral to the aiming arm is expected to induce a reaction time delay, while TMS ipsilateral to the aiming arm should have little effect. The reason for this is that only the contralateral hemisphere is involved in the control of the aiming arm (experiment 1). The effect of ipsilateral and contralateral TMS on the mirroring arm, however, should depend both on the movement condition and the arm that is mirroring. To reiterate, the present hypothesis holds that the right hand is controlled by the contralateral (left) hemisphere regardless of whether the task involves an aiming or a mirroring movement. The left hand, however, is hypothesized to be controlled by the contralateral (right) hemisphere when aiming, and the ipsilateral (left) hemisphere when mirroring. If this hypothesis is correct, only contralateral TMS should influence reaction time of the right arm, regardless of whether it is performing an aiming or mirroring movement. In contrast, left arm movements should be delayed by contralateral TMS when executing an aiming movement, while ipsilateral TMS should induce delays when mirroring movements are performed. The expected effects of TMS on each arm are presented in figure 4.1.

At present, only one other study has used TMS in a reaction time paradigm to investigate the hemispheric control of bilateral movements (Foltys et al., 2001). The authors argued that if one hemisphere dominates the control of both hands during bilateral movements, ipsilateral and contralateral TMS should have differential effects on the left and right hands. Thus, the
Figure 4.1. Predicted effects of TMS for each of the three movement conditions for the left and right arms. (a)-(d) are unilateral movements, while (e)-(f) are bilateral movements. Vertical bars represent reaction time (white = no-TMS, black = TMS). The black arm represents the aiming arm and the gray arm represents the mirroring arm.
Figure 4.1. continued.
hypothesis is very similar to that of the present thesis. To test this, they had subjects perform unilateral and bilateral thumb opposition movements in response to a visual stimulus presented on a computer monitor. Subjects initially performed the task without TMS and then repeated the trials with TMS. The authors reported that the influence of ipsilateral and contralateral TMS on the reaction times of both hands were very similar in the unilateral and bilateral movement conditions. Contralateral TMS produced delays in reaction time in both movement conditions, while ipsilateral TMS had minimal effects. Thus, regardless of whether bilateral or contralateral movements are performed, thumb movements appear to be controlled exclusively by the contralateral hemisphere. However, for a subject with congenital mirror movements, the results were somewhat different. TMS delivered to the hemisphere contralateral to the voluntarily moved limb resulted in delays of both the voluntarily moved hand and the ipsilateral, mirroring hand. This was taken as evidence that the mirror movements resulted from the activation of ipsilateral pathways originating from the hemisphere contralateral to the voluntarily moved hand. Thus, it appears that TMS is able to induce reaction time delays in ipsilateral pathways when those pathways participate in a motor response, although in this study ipsilateral pathways appeared to contribute only to abnormal mirror movements, and not to the control of bilateral movements in normal control subjects.

While the study by Foltys et al. (2001) would appear to raise some doubts as to the potential for ipsilateral control in normal subjects, there are some important differences between their study and those of the present thesis. First, the muscles investigated by Foltys et al. (2001) were intrinsic hand muscles (thenar group) which are much more likely to be under exclusive contralateral control than the more proximal muscles involved in the current
experiments (cf. Brinkman & Kuypers, 1973). This is further supported by the work of Ziemann et al. (1999) who were unable to elicit ipsilateral MEPs from the opponens pollicis muscle—one of the muscles that make up the thenar eminence of the hand investigated by Foltys et al. (2001). Thus, not only did the authors choose a distal muscle likely to be controlled predominantly through contralateral pathways, they additionally selected a muscle, which, relative to other distal muscles such as FDI, appears to have the weakest ipsilateral involvement. As a result of this choice, the authors might have minimized their chances of obtaining evidence consistent with ipsilateral control. Second, the task used in the experiment by Foltys et al. (2001) was very simple. Subjects needed only to perform a rapid thumb opposition movement without emphasis on the quality of the movement performed. However, while the authors note that this may have contributed to their negative results, on the basis of the present hypothesis this would have been expected to maximize the ipsilateral contribution to the left hand. This is because the task does not emphasize movement precision and could therefore be carried out efficiently through ipsilateral pathways. It must be pointed out, however, that this would only be the case if the muscle could be sufficiently controlled through ipsilateral pathways.

One the basis of these issues, we feel that the negative results of Foltys et al. (2001) might reflect the predominantly contralateral control, and relatively weak ipsilateral involvement, of the tested muscle and do not, therefore, preclude the possibility of differential hemispheric involvement for other muscle groups. The present experiments overcome these issues by using tasks involving muscle groups known to receive ipsilateral input (Brinkman & Kuypers, 1973; Ziemann et al., 1999). In addition, by requiring the
movements to be spatially precise, the present experiment addresses the issue of task demands to the relative contribution of the hemispheres in limb control.

4.2. Methods and procedures

4.2.1. Subjects

For the present experiment, both elbow flexion and wrist extension movements were examined. Data were collected from nine subjects for the elbow flexion task (6 female, 3 male, age range 19-36 years) and from eight subjects for the wrist extension task (4 female, 4 male, age range 19-34 years). Six subjects participated in both experiments, one of whom also participated in experiment 2. All participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), were free of neurological and muscular disorders and had normal or corrected to normal vision.

4.2.2. EMG and transcranial magnetic stimulation

For wrist extension movements, pre-amplified, bipolar Ag/AgCl EMG electrodes were attached over the wrist extensor (extensor carpi radialis brevis) and wrist flexor (flexor carpi radialis) muscles of both arms. For the elbow flexion movements, the electrodes were attached over the biceps brachii (long head) and lateral head of the triceps muscles of both arms. A reference electrode was attached over the left lateral malleolus. The EMG signals were amplified (X2000, Therapeutics Unlimited model 544), band-pass filtered (20 Hz to 4000 Hz) and sampled at 2000 Hz using a 12 bit A/D converter. The recorded signals were stored on computer for analysis offline.
4.2.2.1. TMS procedures

TMS was delivered using a Magstim 200 stimulator (Magstim Co. Ltd., UK) connected to a figure-of-8 coil (7 cm outer diameter of each loop). The coil was held tangential to the skull with the handle pointing posteriorly. This orientation induces an electrical current in the brain that travels in the antero-posterior direction and has been reported to be the most effective for trans-synaptic activation of motor cortical neurons (Werhan et al., 1994). The optimal site for evoking MEPs was determined by moving the coil in 1 cm steps along a 4 cm by 4 cm grid positioned over each hemisphere using a moderately suprathreshold stimulus intensity. A schematic of the grid placement and coil orientation are presented in figure 4.2. For the wrist extensors, the muscle was relaxed during this process while active contraction was maintained for the biceps brachii (approximately 5% MVC). The different procedure for the two muscle groups was necessary as it is generally more difficult to elicit MEPs at rest from the biceps muscle (Ferbert et al., 1992). Tonic contraction increases cortical excitability and therefore the ability to evoke MEPs. The optimal site was defined as that coil position that consistently elicited the largest MEPs. Once the optimal location was determined in both hemispheres, the intensity of TMS to be used during the experiment was determined. This process differed slightly for the wrist extensors and biceps brachii and each will be discussed separately.

For the wrist extensors, test intensity was determined relative to resting threshold. Resting threshold was defined as the minimum stimulator intensity able to evoke at least 4 MEPs exceeding 50 μV peak-to-peak out of eight consecutive trials. The stimulator was initially set to a subthreshold intensity and blocks of eight trials were delivered. Following each block of trials, the intensity was increased in increments of 5% of maximal stimulator
Figure 4.2. Grid and coil orientation used for TMS.
output and the process repeated until the threshold level was obtained. This process was carried out separately for each hemisphere.

Once threshold was determined for each hemisphere, an additional block of eight trials was given to the hemisphere with the lower threshold with intensity set to 110% of the threshold. The trials were averaged and the peak-to-peak amplitude of the average MEP was determined. The coil was then re-positioned over the optimal site on the opposite hemisphere and blocks of eight stimulations were delivered. Intensity was adjusted until the peak-to-peak amplitude of the averaged MEP for a block of trials approximately matched that of the averaged MEP obtained from the opposite hemisphere (left 249 µV, +/- 318, right 280 µV, +/- 337). The amplitudes of the two sides did not differ significantly, $t(7) = 1.36, p > 0.2$. An example of the matched MEPs for one subject is presented in figure 4.3a.

Because it can be difficult to obtain MEPs at rest in the biceps brachii (Ferbert et al., 1992), test intensity was determined with the subject maintaining a low level tonic contraction. The subject was asked to hold a light weight in the hand contralateral to the stimulated hemisphere with the elbow flexed to approximately 90°. Test intensity was defined as that intensity, at the optimal location, which yielded an averaged MEP (n = 8 trials) with a peak-to-peak amplitude between 500 µV and 1500 µV. Once an MEP within this range was obtained from one hemisphere, the coil was repositioned over the optimal location of the opposite hemisphere, and the intensity adjusted, until the averaged MEP (n = 8 trials) approximately matched that for the contralateral hemisphere (left 898 µV, +/- 373; right 1000 µV, +/- 385).

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4 For one subject test intensity was determined in the same manner as for wrist extensors.
Figure 4.3. Examples of matched MEPs for (a) wrist extension movements and (b) elbow flexion movements. Note the different voltage calibrations.
right 913 μV, +/- 438). The amplitudes of the two sides did not differ significantly, \( t(8) = 0.15, p > .8 \). An example of the matched MEPs for one subject is presented in figure 4.3b.

4.2.2.2. Determining TMS latency

Each subject performed a set of ten practice trials in both the left arm and right arm unilateral movement conditions. Subjects were instructed to react as quickly and consistently as possible and to move as fast and accurately as possible on each trial. Premotor times were obtained from each trial. Because TMS is most effective in delaying reaction time when delivered close to the time of EMG onset (Ziemann et al., 1997), it was important that the stimulus be delivered near the time of each individual subject’s expected time of voluntary muscle activation. The latency was adjusted such that TMS was delivered approximately 30 ms prior to shortest premotor time obtained in the practice trials. This procedure was used to minimize the possibility of EMG activity beginning prior to delivery of the TMS and to ensure that TMS latency was set relative to individual reaction times. This latency was maintained throughout the entire testing session. The minimum TMS latency used was 50 ms as it has been reported that latencies shorter than this can have a facilitatory effect on reaction time due to the auditory ‘click’ accompanying coil discharge (Ziemann et al., 1997).

4.2.3. Apparatus

The manipulanda for both the elbow flexion and wrist extension movements were identical to those used in experiments 1 and 2, respectively.

4.2.4. Procedures

Each subject completed two blocks of 23 trials (20 test trials, 3 catch trials) in each of four movement conditions: unilateral left (UL), unilateral right (UR), bilateral left arm
aiming (BL), and bilateral right arm aiming (BR). The order of the first set of blocks was counterbalanced across subjects and the order of the second set was the reverse order of the first. The TMS coil was positioned over one hemisphere for the first set of blocks and then repositioned over the opposite hemisphere for the second set of blocks. The initial coil position was counterbalanced across subjects. TMS was delivered on half (10) of the test trials, the order being randomly determined. Prior to each condition, one or two practice trials were given to avoid any carry-over effects from the previous condition.

A trial began with an auditory warning signal (200 Hz tone, 200 ms) which was followed by the go signal (1000 Hz tone, 100 ms) after a fixed foreperiod of 1000 ms. Subjects were told to execute their movements both quickly and accurately, and on bilateral trials to ensure that they were to initiating the movements of both arms simultaneously. Following each trial, feedback was provided regarding the movement time and accuracy of the aiming arm. No feedback was provided for the mirroring arm. Trials on which arm movements were initiated less than 100 ms or more than 500 ms following the go signal were discarded on-line as anticipation and lapses of attention, respectively and were subsequently repeated.

4.2.5. Dependent measures

Five dependent measures were analyzed using separate three-way repeated measures ANOVAs. The factors in the ANOVA were hand (left, right), movement condition (unilateral UN), bilateral left-aiming (BL), bilateral right-aiming (BR)) and stimulus condition (no TMS, ipsilateral TMS, contralateral TMS). The dependent measures were premotor time (PRT, median and mean), movement distance (MD), movement time (MT), variable error (VE). Premotor time was determined using the same procedure as for
experiments 1 and 2. All kinematic measures were determined in the same manner as for experiments 1 and 2 and were based on the initial impulse phase.

4.2.6. Data analysis

The values for each dependent measure for the wrist extension and elbow flexion tasks were submitted to separate three-way repeated measures ANOVAs. Values for the no-TMS conditioning were obtained by combining the trials from both sets of blocks (contralateral-TMS and ipsilateral-TMS). Post-hoc testing was performed using the same procedures as for experiments 1 and 2.

4.3. Results for wrist extension

4.3.1. PRT

The hypothesis of the present experiment was that TMS, delivered immediately preceding voluntary muscle activation, would delay reaction time when it was over the motor cortex controlling the arm. Because the movement conditions are assumed to influence the hemispheric control of the arms, the effect of TMS ipsilateral or contralateral to a given hand was expected to be dependent on the particular movement condition being performed. Because the right arm is expected to be under the control of the left-hemisphere, regardless of the movement condition, only contralateral TMS should increase right-arm PRT. This should also be the case for the left-arm when it is aiming (UL and BL conditions), as the requirement to perform a precise movement restricts control to the contralateral hemisphere (experiment 1). However, in the BR movement condition, the left-arm is expected to come under the control of the left (ipsilateral) hemisphere. If this is correct, ipsilateral TMS should delay PRT for the left arm, while contralateral TMS should have little effect. This would produce an interaction between movement condition and stimulus condition for the left arm,
but only a main effect of stimulus condition for the right arm leading to a significant third-order interaction in the overall ANOVA.

Considering median PRT first, the third-order interaction was not significant, $F(4, 28) < 1$. Thus, the interaction between stimulus and movement condition did not differ for the left and right arms. None of the three second-order interactions were significant. PRT for the left and right hands did not differ across the movement conditions, $F(2, 14) = 1.0$, $p > 0.05$, or across stimulus conditions, $F(2, 14) = 1.9$, $p > 0.05$ and there were no differential effects of stimulus condition for each movement condition, although this effect approached a conventional level of significance, $F(4, 28) = 2.4$, $p = 0.08$. The main effect of hand was also not significant, $F(1, 7) < 1$, indicating that overall, PRT for the left and right hands did not differ.

The main effect of stimulus condition was significant, $F(2, 14) = 18.4$, $p < 0.01$, as was the main effect of movement condition, $F(2, 14) = 7.6$, $p < 0.05$. These effects are presented in figure 4.4. Post-hoc analysis revealed that PRT was significantly increased when TMS was delivered contralateral (129.7 ms, +/- 17.8) to the responding arm compared with both the ipsilateral (108.2 ms, +/- 17.9) and no TMS (107.2 ms, +/- 22.5) conditions, which did not differ. These results are consistent with previous studies involving unilateral movements (Day et al., 1989), and with the study of Foltys et al. (2001) for bilateral movements and indicate that the TMS protocol was sufficient to induce delays in reaction time. That ipsilateral TMS had no significant effect on PRT suggests that the ipsilateral hemisphere was not involved in the initiation of the movement, regardless of movement condition and hand.

Post-hoc analysis of the condition main effect revealed that BL movements (118.8 ms, +/- 19.8) had significantly longer reaction times than both UN (112.0 ms, +/- 16.6) and BR
Figure 4.4. Median premotor time plus standard error for the main effects of (a) movement condition and (b) stimulus condition. PRT was increased when BL movements were performed and when contralateral-TMS was delivered.
(114.3 ms, +/- 18.9) movements, which did not differ significantly. This is consistent with both experiment 2 and our earlier study (Garry & Franks, 2000).

The analysis of mean PRT revealed a pattern similar to that that obtained for median PRT. The main effect of stimulus condition was significant, $F(2,14) = 17.7, p < 0.001$, as was the main effect of movement condition, $F(2,14) = 13.0, p < 0.05$. Additionally, the second-order interaction of stimulus position and movement condition was also significant, $F(4,28) = 4.7, p < 0.01$. Inspection of figure 4.5 reveals that the interaction was largely due to the homogeneity of PRT across movement conditions when contralateral TMS was delivered. Considering first the effect of movement condition at each stimulus condition, post-hoc tests revealed that BL (119.4 ms, +/- 22.8) movements had significantly longer reaction times than UN (106.2 ms, +/-20.4) movements in the no-TMS condition. None of the other means differed significantly although the difference between UN (105.2 ms, +/- 16.3) and BL (115.9 ms, +/- 20.6) movements did approach significance when TMS was delivered ipsilaterally ($t$-critical = 4.24, $t$-obtained = 4.21). Thus, movement condition was able to influence reaction time only in the no-TMS and ipsilateral-TMS movement conditions, but not when contralateral-TMS was delivered.

4.3.2. MD

There were no significant main effects or interactions for movement distance. Figure 4.6 presents the mean movement distance of the left and right hands in each of the three movement conditions. As with the previous experiments, aiming movements were terminated very close to the target region. Although there was a tendency for the left hand to overshoot the target in the BR movement condition, this increase was not significant as indicated by a non-significant hand by movement condition interaction, $F(2,14) < 1$. 
Figure 4.5. Mean premotor time (PRT) plus standard error for the interaction involving stimulus condition and movement condition for wrist extension movements. PRT was longer with contralateral TMS. When contralateral-TMS was delivered (CN), there was little effect of movement condition compared with both the UN and IP stimulus conditions.
Figure 4.6. Mean movement distance plus standard error for wrist movements. Aiming movements (left UN, BL; right UN, BR) terminated close to the defined target (45°) while mirroring movements, especially for the left-hand (BR), tended to overshoot.
It is interesting to note that while TMS had a significant influence on reaction time, it did not affect movement distance. This supports the observation of Day et al. (1989) that while TMS disrupts the release of a programmed movement it does not appear to influence the movement itself. Thus, TMS of the motor cortex does not interfere with a motor program, but only delays its release from the motor cortex.

4.3.3. MT

The main effect of stimulus condition, $F(2, 14) = 5.0, p < 0.05$ was significant. From figure 4.7a it can be seen that overall, movements were completed more quickly when TMS was delivered, regardless of whether it was ipsilateral or contralateral, compared with the no TMS condition. However, post-hoc analyses failed to reveal any significant differences between means. Because both stimulus conditions had faster movement times than the non-stimulated trials, this probably reflects a generalized influence of TMS stimulation on movement execution (Romaiguère et al., 1997). The most parsimonious explanation is that the auditory 'click' that accompanies coil discharge produced a modest facilitatory effect on the speed of movement.

The main effect of hand was also significant, $F(1, 7) = 7.3, p < 0.05$. However, this needs to be interpreted in light of a significant hand by movement condition interaction, $F(2, 14) = 5.0, p < 0.05$. While the post-hoc analyses failed to reveal any significant differences among the means a visual inspection of figure 4.7b suggests the interaction is due to an increase in the movement times for both the left and right hands when mirroring movements were executed (left-hand BR condition, right-hand BL condition). This increase in movement time probably reflects the tendency for mirroring movements to travel further in the initial impulse than aiming movements.
Figure 4.7. Mean movement time plus standard error for the main effect of (a) stimulus condition and b) hand by movement condition interaction.
4.3.4. **VE**

Two effects were significant for variable error: movement condition, $F(2, 14) = 6.6, p < 0.01$, and the hand by movement condition interaction, $F(2, 14) = 11.5, p < 0.01$. From figure 4.8 it can be seen that both hands exhibited greater spatial variability when executing a mirroring movement relative to aiming movements, although this was significant only for the right hand. Thus, when the right hand was mirroring the left in the BL movement condition, spatial variability was significantly higher compared with performance in the UN and BR movement conditions. VE of the left and right hands did not differ significantly for unilateral movements. This increase in variability could result from either the lack of feedback for the mirroring hand, but may also reflect a reduction in monitoring of the mirroring hand in order to emphasize the accuracy of the aiming hand.

4.4. **Results for elbow flexion movements**

4.4.1. **PRT**

The failure for ipsilateral TMS to have an effect on wrist extension movements might be explained by the less prominent ipsilateral involvement in these muscles (Brinkman & Kuypers, 1973). Thus it might be expected that more proximal muscles, such as the biceps, would be more likely to show evidence of ipsilateral control. However, the results for elbow flexion movements were nearly identical to those for wrist movements. Only two effects were significant for median PRT; the main effect of stimulus condition, $F(2, 16) = 9.3, p < 0.01$, and the main effect of movement condition, $F(2, 16) = 5.2, p < 0.05$. As for wrist extension movements there was no evidence that ipsilateral and contralateral TMS had any differential effects on the reaction times of the left and right hands across any of the three
Figure 4.8. Mean variable error plus standard error for wrist extension movements. Mirroring movements (left BR and right BL) were more variable than aiming movements.
movement conditions. This was reflected by a non-significant third-order interaction, 
$F(4,32) < 1$.

PRT was greatest when TMS was delivered contralaterally (151.9 ms, +/- 29.7) compared with both the ipsilateral TMS (140.1 ms, +/- 27.3) and no TMS (139.1 ms, +/- 24.6) conditions (see figure 4.9b). The magnitude of the TMS induced delay in reaction time was smaller than that observed for wrist movements and probably reflects an overall lower TMS intensity as a result of the different method used to determine test intensity. Movement condition affected PRT in a similar manner to that observed for wrist movements (see figure 4.9a). Overall, reaction times were longer for BL movements (150.3 ms, +/- 31.4), than for UN (140.3 ms, +/- 25.8) and BR (140.7 ms, +/- 23.8) movements. However, none of the means differed significantly according to the post-hoc tests.

For mean PRT, the main effect of stimulus condition, $F(2,16) = 6.9, p < 0.01$, was significant while the main effect of movement condition just failed to reach a conventional level of significance, $F(2,16) = 3.3, p = 0.07$. As for wrist extension, the movement condition by stimulus position interaction was significant, $F(4,32) = 2.7, p < 0.05$, similar to that obtained for wrist extension movements. From inspection of figure 4.10 it appears that, as with wrist extension movements, there was a relative insensitivity to movement condition when contralateral TMS was delivered. While overall BL movements had longer reaction times than both UN and BR movements, in the no-TMS and ipsilateral-TMS conditions, this pattern was not apparent when contralateral-TMS was delivered. However, this must be considered cautiously as the post-hoc analysis did not reveal any significant differences among the movement conditions. Analysis of the effect of stimulus condition revealed a significant difference only between no-TMS (140.5 ms, +/- 27.7) and ipsilateral-TMS (133.2
Figure 4.9. Median premotor reaction time (PRT) plus standard error for elbow flexion movements. (a) Main effect of movement condition, and (b) main effect of stimulus condition (both $p < 0.05$). PRT was greater for BL movements and with contralateral-TMS.
Figure 4.10. Mean PRT movement condition by stimulus interaction ($p < 0.05$) for elbow flexion movements. As for wrist movements, the effect of movement condition was reduced when contralateral-TMS was delivered.
ms, +/- 24.5) when UN movements were performed. No other differences were significant. The decrease in reaction time with ipsilateral-TMS has been reported previously (Romaiquier et al., 1997) and might represent a facilitatory effect of the TMS due to the auditory click.

4.4.2. MD

For aiming movements, the initial impulse terminated very close to the target region. Mirroring movements, on the hand, had a tendency to overshoot the target region (see figure 4.11). Despite a tendency to overshoot when executing mirroring movements, there were no significant main effects or interactions for movement distance. Again, this provides support for the conclusion of Day et al. (1989) that TMS only influences the time of release of a programmed movement and does not influence the program itself.

4.4.3. MT

Unlike movement distance, several effects were significant for movement time. There was a significant main effect of stimulus condition, \(F(2,16) = 8.8, p < 0.01\), which resulted from movement times being reduced when TMS was delivered (ipsilateral-TMS = 325.2 ms, +/- 63.2; contralateral-TMS = 325.6 ms, +/- 63.7) relative to the no-TMS condition (342.0 ms, +/- 58.2) (see figure 4.12a). Because the shortening of movement time was observed for both ipsilateral and contralateral TMS, the most parsimonious explanation is that this reflects a generalized facilitation resulting from the auditory 'click' associated with discharging the coil (Romaiquier et al., 1997).

The main effect of movement condition was also significant, \(F(2,16) = 5.4, p < 0.05\), however, this should be interpreted in the context of a significant hand by movement
Figure 4.11. Mean movement distance plus standard error for the left and right hands.
Figure 4.12. Mean movement time and variable error plus standard error. (a) Movement time main effect of stimulus condition ($p < 0.05$), (b) movement time interaction of hand and movement condition ($p < 0.05$), and (c) variable error interaction of hand and movement condition ($p < 0.05$).
condition interaction, \( F(2,16) = 5.3, p < 0.05 \). For both hands, movement times were longer when mirroring movements were performed (see figure 4.12b). However, only the difference between the BR and UN movement conditions for the left hand reached significance. Thus, as for wrist movements, mirroring movements, overall, took longer to execute than aiming movements.

4.4.4. VE

Only the second-order interaction of hand and movement condition was significant for variable error, \( F(2,16) = 15.3, p < 0.001 \). Overall, both hands were more variable in movement termination when performing mirroring movements than when performing aiming movements (see figure 4.12c). Post-hoc analysis revealed that this tendency was significant only for the right hand which exhibited greater spatial variability in the BL movement condition (3.8 degrees, +/- 1.0) compared with the BR movement condition (2.5 degrees, +/- 0.7). There were no significant differences in endpoint variability between the hands either for unilateral or bilateral aiming movements.

4.5. Discussion

The present experiment used TMS in order to directly test the hemispheric involvement in movement initiation in unilateral and bilateral spatially constrained movements. We argued that if BR movements are initiated by a single hemisphere, TMS delivered over that hemisphere should transiently disrupt cortical processes leading to an increase in the reaction time of both arms simultaneously. In contrast, TMS of the uninvolved hemisphere should have little effect on the reaction time of either arm. For BL and UN movements, TMS should interfere with movement initiation of the contralateral arm only, as only the
contralateral hemisphere is expected to be involved in movement initiation for these conditions.

Considering only the overall effect of movement condition on reaction time, the results of the present experiment are consistent with the hypothesized model of control. For both wrist extension and elbow flexion movements reaction times were greater overall when BL movements were performed compared with both UN and BR movements. If, as has been suggested, transcallosal inhibition is responsible for the increases in reaction time when bilateral movements are performed, the data suggest that inhibition is expressed only when the BL movements are performed. The failure for reaction time to increase when performing BR movements indicates initiation of both arms from a single (left) hemisphere.

While it is certainly satisfying that reaction time was influenced by movement condition in a manner consistent with both our earlier study (Garry & Franks, 2000) and with experiment 2, this was not the most important aspect of this experiment. The critical feature was how TMS, delivered ipsilaterally and contralaterally, would affect reaction times. Despite reaction times, overall, being consistent with our hypothesis, the influence of TMS stimulation reveals a picture of control inconsistent with this model.

Regardless of movement condition, only contralateral TMS was able to consistently increase reaction time. Ipsilateral TMS was unable to induce reaction time delays for either arm movements or wrist movements. Because contralateral TMS induced similar reaction time delays in both sides, regardless of movement condition, it would appear that the contralateral hemisphere always participates in movement control. This corroborates the conclusions of both Day et al. (1989) and Foltys et al. (2001) who, using TES and TMS respectively, observed effects only in the contralateral limb when bilateral movements were
performed. Thus, it does not appear that alterations in the hemispheric control of the arms, as postulated in this thesis, can account for the consistently greater reaction times in the BL movement condition relative to the UN and BR movement conditions. If this is correct, the obvious conclusion is that regardless of whether proximal or distal muscle groups are used, and regardless of the movement condition, the motor cortex in both hemispheres always participate in movement initiation when bilateral movements are required. The question that must now be addressed is what the mechanism responsible for the increase is likely to be.

Prior to undertaking this discussion, however, it is worthwhile asking whether the negative results obtained in this experiment might in some way be related to the methodology used. In other words, is it possible that the TMS protocol was simply unable to influence the ipsilateral pathways sufficiently to reveal their involvement in response initiation?

Reviewing the studies of Wasserman et al. (1991, 1994) and Ziemann et al. (1999), it appears possible that the current protocol might not have been able to directly influence the ipsilateral pathways. In each of these studies, TMS was able to evoke ipsilateral MEP responses, both in distal hand muscles and in proximal muscles of the upper arm and shoulder. Thus it is clear that TMS is able to access these pathways. However, to obtain excitatory responses, TMS intensity needed to be very high. In the case of Wasserman et al. (1994) the stimulator was adjusted to 100% of its maximum output, which is considerably higher than the intensities used in the present experiment. In addition, ipsilateral responses are difficult to observe when the muscle is at rest. Subjects generally have to maintain an active contraction before any MEP can be obtained. In this experiment, while contralateral MEPs were readily obtained in all subjects, ipsilateral MEPs were not observed. Hence it
might be argued that TMS intensities adopted in this experiment were simply too low to have any effect.

An additional concern is that the optimal site for evoking ipsilateral MEPs does not coincide with the optimal site for evoking contralateral MEPs. For hand muscles, the cortical region for obtaining ipsilateral MEPs lies lateral and anterior to the optimal location for contralateral MEPs (Wasserman et al. 1994). Thus, not only might the intensity of TMS used have been too low, positioning the coil at the optimal site for eliciting contralateral MEPs could have negated the possibility for inhibiting the ipsilateral pathways.

At first glance, the preceding argument might raise concern that the protocol adopted was insufficient for its intended purpose. It certainly seems that a case can be made for this. However, these challenges to the protocol can be dealt with. First, the preceding argument assumes two things: (1) that the optimal site for eliciting MEPs, either ipsilateral or contralateral is also the optimal location for delaying reaction time, and (2) that the magnitude of the evoked MEP will be directly correlated with the magnitude of the inhibition (reaction time delay) obtainable. While there is evidence to suggest that the optimal location for eliciting contralateral MEPs and inducing contralateral reaction time delays are closely matched (Taylor et al., 1995), the optimal site for activating ipsilateral inhibitory mechanisms does not directly overlap the area for evoking ipsilateral MEPs (Wasserman et al., 1994). While the map for eliciting ipsilateral MEPs tends to be lateral to that for contralateral MEPs, the area for inducing an ipsilateral EMG silent period (a temporary quiescence in active muscle) lies more medial and within the optimal area for evoking contralateral responses. In addition, the TMS intensity required to produce silent periods is lower than that for producing an excitatory response. Thus, to induce inhibition, lower
intensities of stimulation can be used. Because it has been argued that the same neural
circuits mediate reaction times delays and silent periods are the same (Roick et al., 1993;
Romaiguere et al., 1997; Wilson et al., 1995), it is reasonable to assume that both the location
and intensity of stimulation used in this experiment were sufficient to produce reaction time
delays in ipsilateral pathways, if indeed they were participating in the motor response.

With regard to the view that MEP size is related to the magnitude of an induced reaction
time delay, there is little supportive evidence. Romaiguère et al. (1997) measured MEP
amplitudes across trials and correlated them with reaction time. The obtained correlation
coefficient was –0.02 and did not even approach significance. Additional indirect evidence
comes from studies examining the relationship between MEP amplitude and TMS induced
silent period duration. Neither Wilson et al. (1995) nor Triggs et al. (1993) observed a
significant relationship between these two factors. The conclusion is that these two
physiologic responses (MEPs and silent period) reflect the action of different sets of neurons,
and that the neural processes mediating reaction time delays are the same ones mediating
silent period duration (Roick et al., 1993).

From the preceding discussion it can be concluded that the TMS protocol adopted was
sufficient to influence ipsilateral motor pathways, if they were in fact participating in the
motor response. However, even if this were not the case, the protocol would still be suitable
to indirectly implicate ipsilateral involvement. If the ipsilateral pathways were to subsume
control of the ipsilateral arm, the contralateral hemisphere would not participate in the
response. While stimulation of the ipsilateral hemisphere might be insufficient to induce a
reaction time delay, contralateral stimulation would be equally insufficient, as the
contralateral hemisphere would no longer participate in movement initiation. Thus,
contralateral stimulation would induce reaction time delays only in those conditions where the contralateral hemisphere participated in the response, and no delay would be obtained in conditions where control was exerted through ipsilateral pathways. That contralateral TMS always produced reaction time delays, it must be concluded that control was through contralateral pathways in all movement conditions.

Of course it might be argued that contralateral TMS could delay activation of a muscle via ipsilateral pathways by rendering the motor neuron pool refractory during the post-MEP period. If this were the case, delays in reaction time observed with contralateral TMS would reflect spinal inhibitory mechanisms as opposed to inactivation of the controlling hemisphere. While this may be possible theoretically, studies of spinal excitability following TMS suggest this is unlikely. Ziemann et al. (1997) observed that F-wave amplitudes remained relatively unchanged following TMS, and in fact demonstrated an increase in amplitude prior to muscle activation. Roick et al. (1993) tested H-reflexes during the early phase of the silent period and reported an increase in H-reflex amplitude consistent with facilitation of the motor neuron pool (although it might also indicate a decrease in the level of presynaptic inhibition). Thus, it does not seem likely that contralateral TMS could mask involvement of ipsilateral pathways through inhibition of the motor neuron pool.

Given that TMS stimulation did not reveal any evidence of ipsilateral control for either bilateral movement task (BR or BL) what insight does it offer into the control of these movements? In this regard, the interaction between stimulus condition and movement condition for wrist movements is informative. The source of the interaction was a relative insensitivity of PRT across movement conditions when TMS was delivered contralaterally. In the no-TMS and ipsilateral-TMS conditions, movement condition was a significant source
of variation for PRT. However, there was little effect of movement condition when TMS was delivered to the contralateral motor cortex. This might suggest that the movement condition effect is mediated by neural interactions outside primary motor cortex. Before embarking on an attempt to implicate a specific neural structure, it is worthwhile to consider the logic behind this statement.

To simplify this portion of the discussion we will assume only two broadly defined cortical regions: primary motor cortex and ‘extra-motor areas’. For present purposes, the extra-motor areas can be loosely defined as all cortical areas that participate in movement production, beginning from the presentation of the imperative stimulus, up to the point where the primary cortex is activated to release the motor command. In this very general model, the extra-motor areas participate early in the movement initiation sequence, while the primary motor cortex becomes involved late in the sequence.

According to the model proposed in this thesis, the primary motor cortex is the locus of the increase in reaction time in the BL movement condition (as a result of inhibitory callosal interactions). This means that the primary motor cortex takes longer to release the motor command when a BL movement is performed compared to UN and BR movements. This is represented graphically in figure 4.13a. In this figure, the white bars represent activity in extra-motor areas, while the black bars represent activity in the primary motor cortex. The length of each bar indicates the time during which each area is active. Reaction time is therefore the sum of the lengths of the two bars. In figure 4.13a, the effect of movement condition is displayed. Notice first that the activation time of the extra-motor areas is constant across the three movement conditions, while in the BL condition, the time of primary motor cortex activation is lengthened. The result is an increase in total reaction time
Figure 4.13. Comparison of primary motor cortex (a, b) and premotor cortex (c, d) models of movement condition effect. The primary motor cortex model assumes that movement condition influences the processing time in primary motor cortex (black bars). The premotor cortex model assumes that the increase in reaction time occurs in the premotor cortex (white bars). When TMS (arrow) is applied in the primary motor cortex model (b) the effect of movement condition is still observed. In the premotor cortex model, the effect of movement condition is ‘absorbed’ (hatched bars) by the TMS induced delay in primary motor cortex.
in this movement condition. Figure 4.13b represents the same movements conditions when TMS is applied to primary motor cortex. The arrow indicates the time at which TMS is delivered. The gray bars represent the length of the delay induced by the stimulation. If the motor cortex is the locus of the reaction time increase, then it might be expected that the effect of movement condition on processing time would still be present following the TMS induced delay. The result would be overall longer reaction times compared with the no-TMS condition, but a similar effect of movement condition. However, this is not what was observed in the present experiments.

Perhaps, then, the locus of the reaction time increase is not in the primary motor cortex, but in the extra-motor areas. In this scenario, presented in figure 4.13c, the processing time in primary motor cortex is unaffected by movement condition, while processing time for the extra-motor areas increases in the BL movement condition. When the movements are performed without TMS, this model predicts the same results as the primary motor cortex model. However, the prediction is quite different when TMS is delivered. In figure 4.13d, TMS is delivered over the primary motor cortex at the same time as in figure 4.13b. In the UN and BR movement conditions this coincides with the end of extra-motor area activity and the beginning of primary motor cortex activity. As indicated by the gray bars, this induces a delay in primary motor cortex processing leading an overall increase in reaction time. When BL movements are performed, however, the processing time in the extra-motor areas is increased. This means that the TMS induced delay in primary motor cortex will begin before processing in extra-motor areas has been completed. As a result, there will be an overlap in the TMS delay in the primary motor cortex and the activity in extra-motor areas. This is indicated by the hashed region in figure 4.13d. If the TMS induced delay is still present
when processing in the extra-motor areas is completed, the effect of movement condition on reaction time will not be observed since the primary motor cortex will be able to become active. In other words, the TMS induced delay will absorb the effect of movement condition with the end result being an interaction between movement condition and stimulus condition. The question now is which specific brain region might account for this effect?

In a recent experiment, Schluter et al. (1998) studied the effects of TMS stimulation at different latencies over three different brain regions: anterior premotor cortex, dorsal premotor cortex and primary motor cortex. Subjects were required to perform a choice reaction time task to press a computer key with either the index or middle finger of the right hand depending on the shape of a presented visual stimulus. TMS was delivered over the left-hemisphere contralateral to the responding hand. For each of the three sites, reaction time was delayed by TMS. However, maximal delays occurred at different latencies in these areas. Reaction time was delayed with TMS over the anterior premotor cortex 140 ms following stimulus presentation. Over the dorsal premotor cortex, the optimal delay was 180 ms, while over the primary motor cortex the optimal delay was 220 ms. These results indicate that processing of the go signal occurs earliest in premotor cortex, first anterior than dorsal, and then moves to the primary motor cortex. Assuming this same 'stream' of processing occurs for the movements in the present experiment, this implies that the delay of reaction time in the BL movement condition might result from different processing in the premotor areas.

In support of this argument is a recent study by Gomez et al. (2000) that monitored the activity of single cells in the dorsal premotor area of monkeys performing visually guided aiming movements. The movements were visually cued and involved reaching the arm in
one of eight directions to one of six different sized targets. The intent of the study was to determine if neurons in the premotor cortex coded for target size and if they were therefore involved in the execution of spatially constrained arm movements. The results showed an increase in activity in premotor neurons that was dependent on target size. Thus, the control of spatial precision appears to be handled, at least in part, by this brain region. But how does this relate to the differences in reaction time for movements requiring left arm and right arm precision?

One possibility is that the requirement for left-hand precision demands activity of the premotor areas in the right hemisphere not required for movements emphasizing right-hand precision. Considering that the left-hemisphere preferentially dominates in the control of bimanual movements (Peters, 1994), this might require a suppression of the left-hemisphere’s contribution to left-hand control leading to an increase in reaction time. In other words, prior to initiating the movement, the right-hemisphere inhibits the left to reduce the potential of interlimb interference. This argument is very similar to the transcallosal inhibition hypothesis although it puts the locus of inhibition at an earlier stage of processing than the motor cortex. Consistent with this interpretation are reports of unwanted associated movements accompanying left-hand performance following damage to the corpus callosum (Geschwind et al., 1995). Additionally, there are reports of split-brain patients reducing left-hand usage due to interference from the right hand (Preilowski, 1975). Thus, without an intact corpus callosum, the ability of the right hemisphere to suppress the left-hemisphere is impaired leading to undesirable left-hemisphere involvement.

In a related vein, it is interesting to note that asymmetrical arm movements are associated with even greater increases in reaction time than simple symmetrical arm
movements (Stelmach & Worringham, 1988), even when there is no emphasis on movement precision. In a study by Taniguchi et al. (1977) subjects were required to perform unilateral elbow flexion or elbow extension movements, or bilateral movements involving simultaneous flexion, simultaneous extension or flexion of one arm and extension of the other. While the reaction times for bilaterally symmetrical arm movements differed statistically from unilateral movements, the mean difference was very small (~2 ms). In contrast, reaction times for bilaterally asymmetrical movements were substantially larger (~13 ms) and differed significantly from both unilateral and bilateral symmetrical movements. Stelmach and Worringham (1988) also compared symmetrical and asymmetrical movements using a bilateral aiming task. In this study, however, symmetrical and asymmetrical movements differed only in terms of movement amplitude, not direction. While symmetrical movements had significantly longer reaction times than unilateral movements, asymmetrical movements had even greater increases in reaction time. An important aspect of these asymmetrical movements is that they require greater hand independence than do symmetrical movements.

Sadato et al. (1997), using positron emission tomography (PET), observed that performing asymmetrical bimanual finger movements requires more activity in the premotor cortex of the right hemisphere relative to unilateral movements. This increase in activity was not apparent when symmetrical finger movements were performed. They suggested the increased activity in the right premotor area might be required to suppress "default" bimanual mirror movements and implicated the corpus callosum in this role. If the right-arm aiming movements used in the present experiments can be considered 'default' mirror movements
and the left-arm aiming movements ‘non-default’ due to the emphasis of left arm precision, a role for the right hemisphere premotor cortex seems reasonable.

This ‘premotor cortex’ model predicts that only tasks requiring involvement of the right premotor cortex will be associated with transcallosal inhibition, and therefore an increase in reaction time. Simple bimanual movements, in and of themselves, would not necessarily lead to a reaction time increase. As it appears that bilateral motor cortex activation accompanies bilateral movements regardless of the task (cf. Foltys et al., 2001), simply executing a bilateral movement would be insufficient to cause this increase. This explains why bimanual aiming movements show increases in reaction time (Kelso et al., 1979, 1983; Marteniuk and others, 1980, 1983; Stelmach & Worringham, 1988), while simple bimanual movements do not (Anson & Bird, 1993; Swinnen et al. 1995; Taniguchi et al., 1977).

The premotor cortex model shares a number of features with our original hypothesis. First, the increase in reaction time accompanying BL movements is postulated to occur through transcallosal inhibition. Second, the reaction time differences between BL and BR movements are due to differences in the participation of the left and right hemispheres. In a general sense, then, this model is not all that different from the original hypothesis. In terms of specifics, however, there are some notable and important changes. First, the muscles of the arms are always controlled through descending pathways originating from the contralateral motor cortex. Although there is substantial evidence that direct ipsilateral control, especially for the proximal arm muscles, is possible (Brinkman & Kuypers, 1973; Jakobson et al., 1994), the data from the present experiment are not consistent with such control. Regardless of whether the task involves distal or proximal muscles, and whether the right or left hand must execute a precise movement, direct muscle activation appears to be
mediated by the contralateral motor cortex. A second difference between this model and our original model is that it suggests bilateral activation of homologous motor areas does not automatically lead to interhemispheric inhibition (cf. Ohtsuki, 1994), at least with regard to the initiation of rapid movements. If bilateral motor cortical activation were sufficient to induce interhemispheric inhibition, increases in reaction time should have been observed for both types of bimanual movements, not only those that require left-hand precision. Thus, while transcallosal inhibition is still considered the process mediating the reaction time increase, it is not considered to be acting between the primary motor areas, but between cortical regions that participate in an earlier stage of processing, most likely the premotor areas.
5. General Discussion

The model of control tested in this thesis was that reaction time increases when bilateral movements are performed due to inhibitory transcallosal interactions. These interactions occur for movements involving the participation of both hemispheres in movement initiation. On the basis of our earlier study (Garry & Franks, 2000), it was assumed that such interactions do not always occur, with the result that bilateral movements do not always yield increases in reaction time relative to unilateral movements. During unilateral and bilateral movements requiring spatial precision of the left arm, arm movements are initiated by the contralateral hemisphere. Hence, these bilateral movements require participation of both the left and right hemispheres at movement initiation leading to increases in reaction time.

When movements requiring right arm precision are performed, however, the left arm was assumed to come under control of the left hemisphere through ipsilateral pathways. In this case, the movements of both arms are initiated simultaneously from the same hemisphere with the result that transcallosal inhibition, and the concomitant increase in reaction time, is avoided.

In experiment 1, it was determined that the requirement to perform a spatially precise movement was sufficient to restrict control to the contralateral hemisphere. Experiment 2 revealed that distal arm muscles, the wrists, were influenced by movement condition in a similar manner as proximal arm muscles, suggesting that they may also be accessible through ipsilateral pathways. This interpretation is consistent with recent neurophysiological studies reporting the existence of ipsilateral pathways for some wrist and hand muscles (Wasserman et al., 1991, 1994; Ziemann et al., 1999). Experiment 3 was designed to directly test the
hemispheric control of the arm and wrist muscles using a combined TMS and reaction time paradigm.

Despite overall reaction times in Experiment 3 being consistent with our proposed transcallosal inhibition, ipsilateral control hypothesis, the effect of TMS on reaction time failed to provide support for the model. Regardless of the arm or movement condition, only contralateral TMS was produced significant delays in reaction time. This was the case for both wrist extension movements and elbow flexion movements. We had expected that when TMS was delivered in the BR movement condition, reaction time delays would have been observed in both arms when the left hemisphere was stimulated, but in neither arm when the right hemisphere was stimulated. Such a finding would have been consistent with ipsilateral control of the left arm when spatial precision was not emphasized. The possibility that the TMS protocol might have been insufficient to yield results consistent with the model was excluded. As a result, the conclusion that must be reached is that regardless of the movement condition, the left and right arms are always controlled by the motor cortex of the contralateral hemisphere. Thus, if transcallosal inhibition is the mechanism responsible for the increase in reaction time when bilateral movements are executed, it must be overcome in some way other than through a reliance on ipsilateral control when the BR movements are performed.

On the basis of recent imaging (Sadato et al., 1997) and single-cell recording studies (Gomez et al., 2000) we suggest that differences in reaction time between the two bilateral movement condition (BL and BR) results from differential activity of the premotor cortex in the right hemisphere. Increased activity in this region has been associated with movements that require spatial precision (Gomez et al., 2000) and those that require independence of the
hands during bilateral task performance (Halsband et al., 2001; Sadato et al., 1997). While it might be argued that the movements used in the present experiment do not require hand independence in the sense of the left and right hands executing different tasks, the need for precise control of the left hand might make these movements functionally similar to those that involve overt independence (e.g., asymmetrical movements). Having to execute spatially precise movements with the left hand might demand the suppression of left-hemisphere premotor areas to minimize interference for the control of the left hand. This suppression probably involves transcallosal pathways (Sadato et al., 1997) leading to a measurable increase in reaction time.

5.1. Implications for studies of the bilateral deficit

While the evidence in support of the bilateral deficit is quite strong (Howard & Enoka, 1991; Li et al., 2000; Ohtsuki, 1981a, 1981b, 1983; Shantz et al., 1989) the results of the present experiments suggest that it is not a global phenomenon inevitably associated with bilateral movements. Although a deficit in reaction time was consistently observed in these experiments, it appeared only under specific conditions (i.e., the BL movement condition). Only when the task emphasized the role of the left-hand were bilateral movements initiated more slowly than unilateral movements. In addition, there was little evidence that bilateral movements led to deficits in movement execution, at least in terms of movement time. Although, there was a tendency for the mirroring hand to require more time to complete the movements during bilateral trials, the aiming hand was relatively unaffected. In addition, the increase in movement time for the mirroring hand can be accounted for by its tendency to travel a greater distance. Hence, the increase in movement time was not due to a relative slowing of the mirroring hand, but an increase in the distance traveled.
For bilateral arm movements, an increase in movement time has been reported when the task requires simultaneous precision of both arms (Honda, 1982; Kelso et al., 1979, 1983; Marteniuk and others, 1980, 1983). Because no such increase was observed in the present experiments it can be concluded that the increase in these other experiments was related to the requirement for simultaneous precision. If the bilateral deficit is mediated by interhemispheric interactions (cf. Ohtsuki, 1994) the differences between the present experiments and those of others imply that such interactions occur throughout the movement when spatial precision is required by both hands, but not when only one hand must be accurate. The increase in reaction time in the BL movement condition suggests that interhemispheric inhibition was occurring at an early stage of movement preparation. However, this interaction appears to be transient and does not influence the kinematic features of the movement itself. This might indicate that there are different mechanisms mediating bilateral deficits in reaction time and movement kinematics, or that there is only one mechanism that acts early in preparation, and if necessary, throughout the movement when feedback processing of both arms is required. If it is interactions between premotor areas that leads to the increase in reaction time, increases in movement time may result from similar interactions occurring throughout the movement, rather than just during movement preparation. In light of this possibility, future studies investigating the bilateral deficit should take into account the nature of the task, as this appears to be an important factor.

5.2. Implications for studies of manual asymmetries

As has been reported previously, the right and left hands of right-handers differ in terms of their relative proficiency in movement initiation and movement execution when unimanual movements are performed. Whereas the left hand typically enjoys a reaction time
advantage, the right hand tends to complete movements more quickly (Bradshaw et al., 1990; Carson et al., 1990; Carson et al., 1995; Elliott et al., 1993; Hodges et al., 1997; Roy et al., 1994). The superior performance of the right-hand for movement execution has been attributed to the left hemisphere’s ability to more efficiently use sensory feedback than the right hemisphere (Elliott et al., 1993). In contrast, the left hand’s advantage in reaction time has been argued to reflect a right-hemisphere specialization for movement planning when the task requires spatial uncertainty (Mieschke et al., 2001). Extrapolating from these studies, one might anticipate a reaction time advantage for bimanual movements emphasizing left-hand precision. From the results of the present experiments, however, this is clearly not the case. In contrast to unimanual movements, bimanual movements requiring left-hand precision appear to be at a consistent disadvantage relative to bimanual movements requiring right-hand precision. The inability of the right-hemisphere to express its superiority for these tasks might be related to the tendency toward left-hemisphere dominance when bimanual movements are required (Peters, 1994).

In everyday tasks, there appears to be a bias toward right-hand dominance and continuous monitoring of the right hand. Recall from that Peters (1994) emphasized four aspects of dominance in bimanual tasks. First, he pointed out that the primary, or focal goal, of the task is executed by the right hand while the left hand assumes a subsidiary, or supportive role. Second, regardless of whether the task is simple or complex, coordination is realized through precise timing of the movement onset of the right hand. Third, the right hand tends to execute movements that require precise control of speed and force. And finally, the right hand tends to receive a continuous allocation of attention while the left hand receives attention intermittently. With respect to the present thesis the final two points are of
interest. Together they suggest that during bimanual movements the right hand 'prefers' to execute the movement requiring precision and that performance of that movement is continuously monitored. In the BL task used in the present experiments, the right hand was completely unable to assume the dominant role. Hence, the right hemisphere might be required to take over. If this is the case, it could lead to a competition between the dominant left hemisphere which 'wants' to guide the movement and the non-dominant right hemisphere which 'has' to guide the movement. Because the BR movement most closely resembles natural tasks (i.e., the right performs the focal movement, requires precise adjustment of force and can be continuously monitored), such interference could be avoided leaving reaction time unaffected.

What is interesting about this is it suggests that asymmetries might exist not only for unimanual movements, but also for bimanual movements. While unimanual movements can easily be defined as 'left' and 'right', it is much more difficult to categorize bimanual movements in this way. However, the tasks used in the present experiments allow a relatively straightforward distinction to be made. As the two hands do not have to work together to complete a common goal, as is the case for bimanual prehension movements for example, there is a clear dissociation between the tasks. BR movements can justifiably be classified as right bimanual movements while BL movements can be classified as left bimanual movements. On the basis of the results from this thesis, it can be tentatively suggested that the manual asymmetries observed for unimanual movements, at least with respect to reaction time, are reversed when bilateral movements are performed. This reversal reflects functional differences in the control of the arms during bimanual movements and
reveals interhemispheric interactions that are not expressed when unimanual movements are performed.

It will be interesting to determine if this reversal holds for other task manipulations as well. For example, the left hand advantage in unimanual movements appears to be most prominent when the location of a target is not specified in advance (Carson et al., 1995). Thus, when the movement cannot be completely preprogrammed prior to the presentation of the ‘go’ signal, the right-hemisphere’s advantage for processing spatial information is maximized. In terms of the present model, this would suggest a greater involvement of the right hemisphere following the ‘go’ signal in conditions where advance information was not available. As a result, it is possible that the interaction between the hemispheres would be even greater under these conditions leading to an even larger deficit for left-hand bimanual movements.

5.3. Future directions

Future work will be directed toward uncovering the relative contribution of the premotor areas of the left and right hemispheres during bimanual movements. One way to do this would be to repeat experiment 3 giving TMS over the motor cortex, as well as over premotor areas. By delivering the stimuli at different times following the imperative stimulus, this paradigm would be able to identify any changes in the contribution of the premotor areas when the role of the left and right hands are reversed.

A recent study (Schluter et al., 1998) has found that stimulation of the left-premotor cortex, but not the right, induces delays in reaction time of both hands during a unimanual choice reaction time paradigm. From this, the authors suggested that the left-premotor cortex might be specialized for the selection of an action. This conclusion is consistent with other
suggestions of left-hemisphere dominance in action (Schluter et al., 2001). At this time, it does not appear that any reaction time studies investigating premotor cortex involvement have been conducted using bimanual movements. If, as has been suggested here, the premotor cortex in the right hemisphere takes on a more prominent role when left-hand, bilateral movements are required, a greater effect of right hemisphere stimulation should be observed for these movements. In addition, if bimanual movements requiring left-hand precision are functionally similar to asymmetrical bimanual movements, comparable results should be obtained between the two tasks. In fact, a simple asymmetrical movement task could be used as an initial testing condition as increased activity of the right premotor cortex has already been observed for these movements (Sadato et al., 1997). As a result, temporary inactivation of the right premotor area should lead to increases in reaction time.
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